Original Paper

Impact of Cognitive Behavioral Therapy on Resting Cardiac Parameters and Cortisol in Patients with Post-Traumatic Stress Disorder: A Pilot Randomized Clinical Trial

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Abstract

Post-Traumatic Stress Disorder (PTSD) has been associated with changes in psychophysiological and neuroendocrinal parameters. Cognitive Behavioral Therapy (CBT) is considered the treatment of choice for PTSD and is able to regularize altered neurobiological parameters; however, little is known about its effects on these parameters when measured during the therapeutic process. This pilot study aimed to evaluate the impact of CBT on cortisol and cardiac parameters measured at rest during the treatment of PTSD with comorbid major depression. 14 patients were randomized to four months of CBT or a waiting list. As expected, the experimental group had a greater reduction in PTSD symptoms and a large effect size. There was a reduction in the low frequency component of heart rate variability, which achieved borderline statistical significance and a large effect size. Salivary cortisol tended to track the progress of therapy, rising in the period of exposure and decreasing by the end of treatment. Despite the small sample size, this study opens the way for further research into the impact of CBT on the different biological markers of PTSD during the therapeutic process. This can hopefully help to optimize and personalize therapeutic studies while providing clues about modifications in bio behavioral pathological manifestations.

Keywords

post-traumatic stress disorder, cognitive behavior therapy, cardiac parameters, cortisol, translational research

1. Introduction

Post-traumatic stress disorder, which is usually associated with a significant impairment of social, work and family life, is a chronic debilitating reaction to a traumatic situation. This reaction involves symptoms of reexperience, avoidance, negative changes in cognition and mood and autonomic hyperarousal (American Psychiatric Association, 2013). Fear processing neural, psychophysiological and behavioral markers (Shvil, 2003) have begun to be investigated in an effort to enable more accurate diagnosis and prognosis, and provide more effective treatments (Singh & Rose, 2009).

Cardiac autonomic dysregulation is considered a psychophysiological marker of PTSD. This disruption can be studied by extracting the sympathetic and parasympathetic components of Heart Rate Variability (HRV) (Berntson et al., 2007). Several studies have shown that a reduction in parasympathetic components is associated with poor general health and increased cardiovascular morbidity and mortality (Tsuji et al., 1996; Dekker et al., 2000; Thayer & Lane, 2007; Nunan et al., 2010). In addition, reduced cardiac parasympathetic function can follow or precede the development of various risk factors, meaning that high parasympathetic activity is a predictor of good health and good autonomic and emotional regulation (Pumprla et al., 2002; Thayer & Lane, 2007; Vanderlei et al., 2009). The most prominent cardiovascular alterations in PTSD include increased heart rate during the presentation of stimuli conditioned to trauma (Peri et al., 2000), increased resting heart rate (Orr, Metzger, & Pitman, 2000), slower heart recovery compared to non-traumatized subjects (Wessa & Florr, 2007; Norte et al., 2013), and decreased heart rate variability when compared to subjects who have been through a traumatic event, but did not develop PTSD (Norte et al., 2013).

The role of cortisol in PTSD has been investigated because it is a hormone activated in response to stress. Its secretion is mainly controlled by the Hypothalamic-Pituitary-Adrenal (HPA) axis, and prolonged activation of the HPA axis has been associated with numerous deleterious effects including obesity, impaired immunity, atherosclerosis, and brain nerve cells atrophy (McEwen, 2003). Research involving PTSD and the HPA system has generated inconsistent results (Morris et al., 2012; Meewisse et al., 2007), possibly due to the variety of methods used and the differences between the investigated samples. For example, PTSD and major depression, which has a comorbidity index of 37% (Breslau, Davis, Andreski, & Peterson, 1991), seems to have a different impact on cortisol activation (Kendall-Tackett, 2000). A meta-analysis on the subject evaluated 47 studies and concluded that baseline morning cortisol levels are lower in patients with PTSD or PTSD comorbid with depression when these groups are compared to subjects who suffered trauma. However, afternoon or evening cortisol levels are lower in PTSD patients compared to non-traumatized subjects, but when there is

comorbid depression, cortisol levels are higher (Morris et al., 2012).

Research into psychophysiological markers leads to a better understanding of the benefits of existing treatments. It is known that Cognitive-Behavioral Therapy (CBT) has documented efficacy in the treatment of PTSD, significantly reducing psychological symptoms (Bisson, 2007); however, little is known about its impact on biological parameters. In a recent meta-analysis, a reduction in heart rate caused by cognitive behavioral protocols administered in patients with PTSD was found (Gonçalves et al., 2015) but no studies were found when biological parameters were assessed at rest rather than during symptom evocation. The objective of this study was, therefore, to evaluate possible cardiac and neuroendocrine changes in PTSD patients during treatment with CBT when they are measured at rest.

2. Materials and Methods

2.1 Sample

14 adults of both genders took part in the study. They were recruited through the media (newspapers, magazines, television and radio) and by the dissemination of information about the treatment to health professionals. Only patients over 18 years old diagnosed with the full criteria for PTSD, according to the Structured Clinical Interview for DSM-IV (SCID), were included in the study. Pharmacological treatment was allowed during the study.

Excluded subjects were those in parallel psychotherapeutic treatment, who met diagnostic criteria for antisocial personality disorder or borderline personality disorder, were addicted to alcohol or drugs, had serious brain conditions, were pregnant or had primary psychosis. The study was approved by the Ethics Committee of the Institute of Psychiatry, Federal University of Rio de Janeiro under the CAAE number 0051.0.249.000-11, and covered the terms of informed consent, questionnaires, treatment protocols and psychophysiological evaluation. Participation in this study was subject to the participants signing a document giving their free and informed consent.

2.2 Procedures

Potential participants were assessed using the SCID by a psychiatrist. Participants who met the inclusion criteria were randomized to active treatment (experimental group) or waiting list (control group). Randomization was performed by sequence numbers randomly generated by software. Both groups had monthly psychometric and psychophysiological evaluations, from one week before the beginning of the therapy/waiting period until the end of therapy/waiting time (pre to month 4, totaling 5 evaluations). The experimental group had an extra evaluation, one month after the end of treatment (follow up). After the waiting period (four months), the same treatment was offered to the control group participants. Figure 1 describes the procedures.
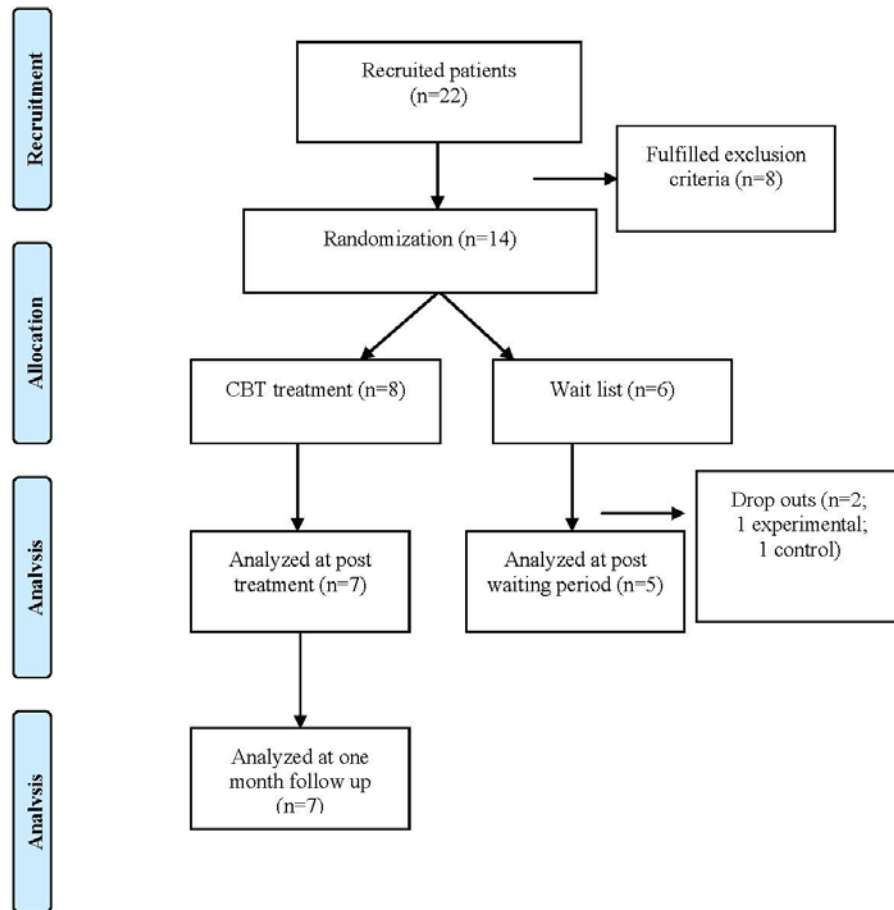
Figure 1. Flow Diagram for the Procedure

After participants signed the free and informed consent form, the first endocrine and cardiac evaluations were conducted, followed by the completion of the psychometric questionnaire. Each stage of data collection was conducted as follows:

The patient was asked not to eat anything for at least an hour prior to their appointment. They were allowed to drink water during this period. After at least five minutes of sitting without any activity, the following steps were taken: (1) endocrine evaluation; (2) cardiac evaluation; (3) general questions: participants responded to four questions: were there any stressful event during that week; what time did he/she go to sleep the day before and wake up on the day of the experiment; which medications were taken on the day of the experiment; and, for women, was she in the menstrual period; (4) psychometric evaluation.

2.2.1 Endocrine Evaluation

Salivary cortisol is considered to be a reliable and valid measure of unbound ("free") cortisol concentration in the plasma. In each evaluation, one unstimulated saliva sample was collected during the experimental session by the use of a cotton swab. Samples were collected for 1 min at rest. Saliva

was extracted from the cotton swab by centrifugation at 5000 rpm for 10 min. Cortisol concentrations were determined by radioimmunoassay using a commercial kit (DIAMETRA).

2.2.2 Cardiac Evaluation

Accurate analysis of HRV can be performed by different methods: in the time domain, the Root Mean Square of Successive Differences (RMSSD) indicates parasympathetic activity; in the frequency domain, High Frequency (HF) is also indicative of vagal influence on the heart, while Low Frequency (LF) is indicative of the vagal and sympathetic components, predominantly sympathetic. For the present study, a computer running Acknowledge (BIOPAC Systems Inc.) software controlled the data acquisition of the electrocardiographic parameters. Electrocardiographic recordings were collected at a sampling frequency of 1000 Hz and at lead II. An off-line peak detection algorithm (derivative plus threshold) was used to estimate fiducial R-wave points, after which the series was screened by hand and corrected for artefacts. Successive RR intervals were estimated in milliseconds. The cardiac parameters were extracted for 10 min and the last 5 min used for the analysis:

- Heart Rate (HR): Correlated to increased sympathetic and decreased parasympathetic activity;
- High Frequency (HF), from 0.15 to 0.4 Hz: a marker of parasympathetic activity;
- Low Frequency (LF), from 0.04 to 0.15 Hz: possibly correlated to sympathetic and parasympathetic activity or to baroreflex sensibility;
- Root Mean Square of Successive R-R interval Differences (RMSSD): a marker of parasympathetic activity.

The data processing followed the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology. The Matlab software (KARDIA) was used to analyse cardiac parameters.

2.2.3 Psychometric Evaluation

The Post Traumatic Stress Disorder Checklist-Civilian Version questionnaire (PCL-C) is a self-administered instrument for assessing symptoms of PTSD. The Brazilian version consists of 17 items scored 1 to 5, which evaluate the diagnostic criteria described in DSM-IV (Berger et al., 2004). The questionnaire was completed individually by the participants. We chose to do the psychometric evaluation after the cardiac and neuroendocrine evaluations due to the possibility of psychopsysiological reactions caused by the emotional charge associated with the content of the questionnaire.

2.2.4 Treatment Protocol

The study used a treatment protocol for patients with PTSD developed by Drs Edna Foa and Barbara Rothbaum (Foa & Rothbaum, 1998). This protocol was adapted for the Brazilian population by Pedrozo (2008). One psychotherapy session and three co-therapy sessions were performed weekly, all of 90 minutes each, resulting in 16 main therapy sessions and 48 co-therapy sessions, over 4 months.

The co-therapy sessions were conducted between the psychotherapy sessions by a psychology student trained and supervised by a qualified psychologist with a PhD degree. The purpose of the co-therapy was to stimulate anxiety management techniques and to conduct in vivo exposure sessions. The treatment was performed as following:

· Session 1: guided PTSD interview, psychoeducation about CBT and PTSD and anxiety management techniques (progressive muscle relaxation and diaphragmatic breathing or polarized breathing).

· Session 2: psychoeducation about PTSD and family session aimed at giving information about the disorder and the therapy.

· Session 3: cognitive restructuring of beliefs related to the traumatic event.

· Session 4: cognitive restructuring of beliefs related to the traumatic event.

· Session 5: psychoeducation about exposure techniques and in vivo exposure hierarchy worksheet.

· Session 6: in vivo exposure and imaginary exposure (listening to a recording of the trauma description).

· Session 7-16: cognitive restructuring, in vivo exposure and imaginary exposure.

· Session 16: relapse prevention.

2.3 Statistical Analysis

Due to the limited number of participants, the statistical significance of differences between groups was obtained through the Kruskal-Wallis test. The effect size (Cohen's d) of the mean differences between groups was also calculated. The results of the mean difference between assessments performed before and after treatment/waiting period will be presented. For evaluations carried out between these periods, we will present a qualitative analysis of the data.

3. Results

3.1 Baseline Evaluation

Seven patients in the experimental group completed the treatment, while five completed the waiting period in the control group. All participants had comorbid major depression, no history of trauma in childhood and were submitted to pharmacological treatment prescribed by psychiatrists of the PTSD ambulatory clinic at the Federal University of Rio de Janeiro, Brazil. The socio demographic data are shown in Table 1:

Table 1. Socio-Demographic Data

Socio demographic data	Experimental group	Control group
Type of trauma		
Motor vehicle accident	2	2
Urban violence	5	3
Gender		
Female	3	2
Male	4	3
Marital status		
Married	2	4
Divorced	5	1
Years of education		
0- 9 years	0	2
9 years	3	2
9-12 years	1	0
12 years	2	1
University education	1	0
Age		
18-30	0	0
31-40	1	1
41-50	4	3
51-60	2	1
Mean	47.43	46.8

3.2 Treatment Adherence

Two participants withdrew from the study, one from each group. The reasons for the dropouts were not related to adverse effects of exposure techniques. All participants who did not withdraw from the study completed all 16 sessions.

3.3 Effects of Treatment

The difference between the average pre and post-treatment/waiting period of the variables, as well as the p value and the effect size, are shown in Table 2.

Table 2. Average Differences between Pre and Post-Treatment (Total Group)/Waiting List, p Value and Effect Size

Variables	Delta pre-post*	Delta pre-post*	P value **	Cohen's *d*	Delta pre-follow up
	Experimental	Control			Experimental
PCL-C	9.71	-1.67	0.5676	0.859	10.2
Cortisol	1.20	-1.51	0.4561	0.638	1.21
Heart rate	-3.55	-3.3	0.8501	0.015	4.69
High Frequency	31.30	-17.81	0.3447	0.54	29.02
Low frequency	15.09	-60.43	0.1859	0.763	58.19
RMSSD	5.75	-2.03	0.2568	0.207	-1.69

*Difference between before and after treatment/waiting period; ** Kruskal-Wallis test

In order to know the real impact of CBT on psychophysiological parameters, we did a separate analysis of the patients who responded to the treatment according to the PCL-C and compared this data to the control group. We defined this group as the subjects that had a minimal decrease of 15 points in the PCL-C. These data are shown in Table 3.

Table 3. Average Differences between Pre and Post-Treatment (Respondents: n=3/waiting list: n=5), p Value and Effect Size

Variables	Delta pre-post*	Delta pre-post**	P value **	Cohen's *d*	Delta pre-follow up
	Experimental	Control			Experimental
PCL-C	18.5	-1.67	0.1573	1.331	10.2
Cortisol	1.28883	-1.51	0.4795	0.575	1.21
Heart rate	-2.29874	-3.3	0.5637	0.408	4.69
High Frequency	44.56896	-17.81	0.2482	0.578	29.02
Low frequency	102.8095	-60.43	0.0833	2.097	58.19
RMSSD	8.65654	-2.03	0.2482	0.323	-1.69

*Difference between before and after treatment/waiting period; **Kruskal-Wallis test

3.4 Psychometric Variable

According to the results of the PCL-C, a recording of the trauma description the experimental group was consistently lower at the end of the treatment, and this reduction was maintained in the follow-up period, one month after the end of treatment. The average decrease was 9.71 points. In the control group, there was also a score decrease; however, the average decrease was 6 points.

One of the patients in the control group had a completely different pattern of response. His PCL-C score decreased 42 points from the beginning to the end of the waiting period. This factor is probably due to the effect of pharmacological treatment. If we remove this outlier patient from the analysis, the control group average PCL-C score increases 1.67 points.

The comparison between the group's average scores before and after treatment/waiting period shows no statistically significant ($p=0.5676$) effect of CBT. However, the effect size was large (Cohen's $d=0.859$) (Figure 2).
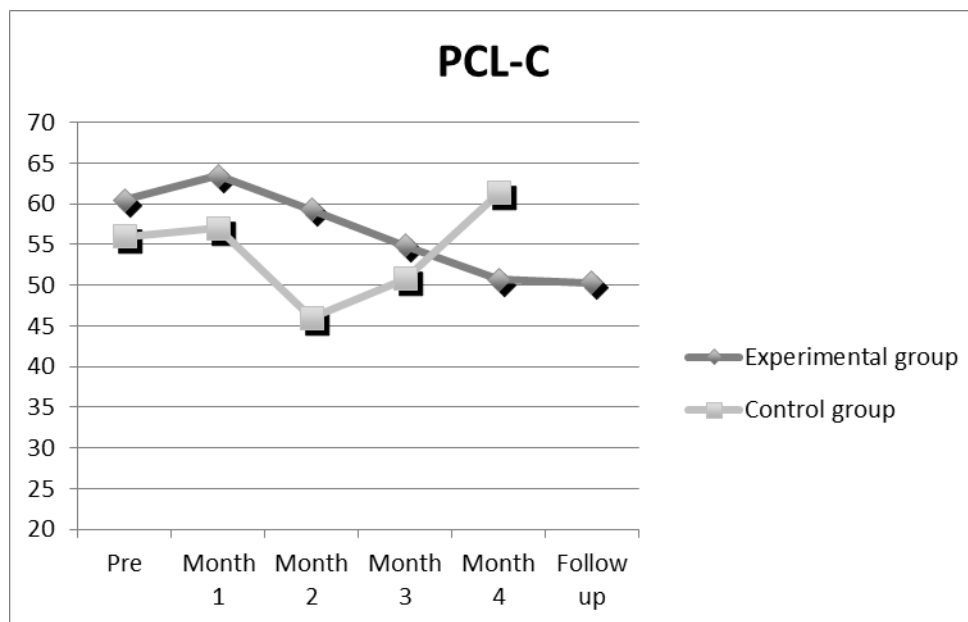
Figure 2. PCL-C Scores throughout the Treatment/Waiting Period

The analysis of patients who responded to the treatment, shows that the result gets closer to statistical significance ($p=0.1573$) and the effect size increases (Cohen's $d=1.331$).

3.5 Cardiac Variables

Data from seven subjects in the experimental group and four in the control group were analyzed.

3.6 Heart Rate

There was no statistically significant difference between the mean heart rate before and after treatment between groups ($p=0.8501$). The effect size was small (Cohen's $d=0.015$). In the experimental group, there was a heart rate decrease only in the follow up period (Figure 3).
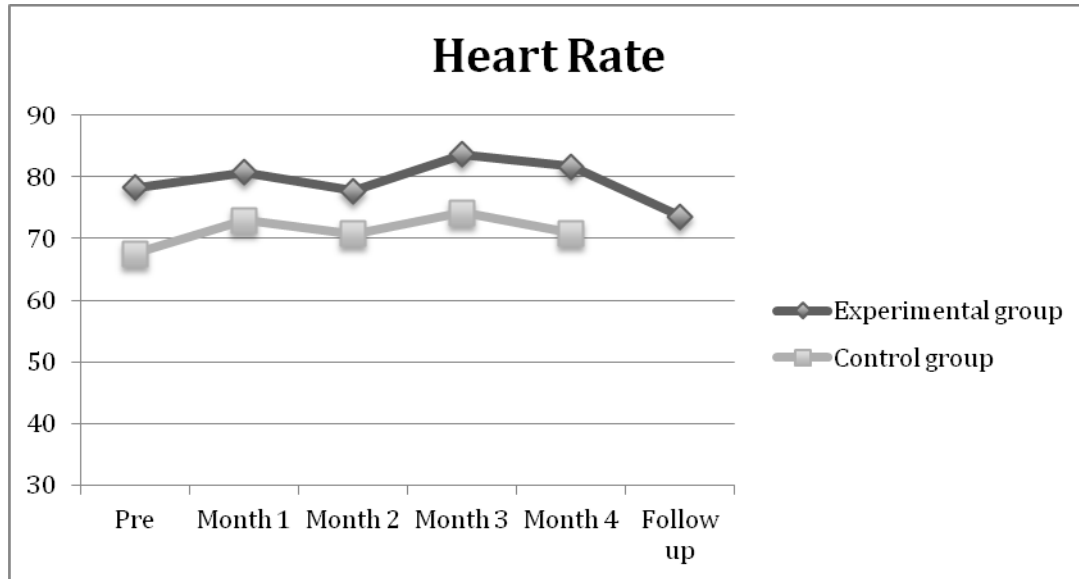
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Figure 3. Heart Rate throughout the Treatment/Waiting Period

An analysis of the treatment responders indicates that the difference between this subgroup and the control group was not significant (p=0.5637) and effect size remained small (Cohen's d=0.408).

3.7 High Frequency

With respect to HF, the difference between the groups' average scores before and after treatment/waiting period was not statistically significant (p=0.3447). The effect size was medium (Cohen's d=0.54). There was a decrease in the experimental group at month 4 and an increase at follow up (Figure 4).
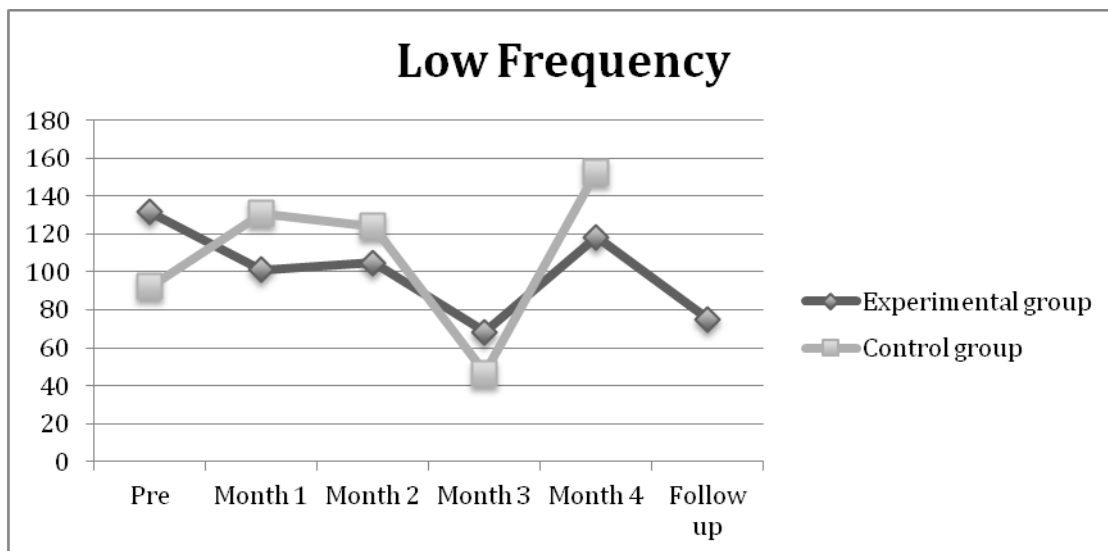
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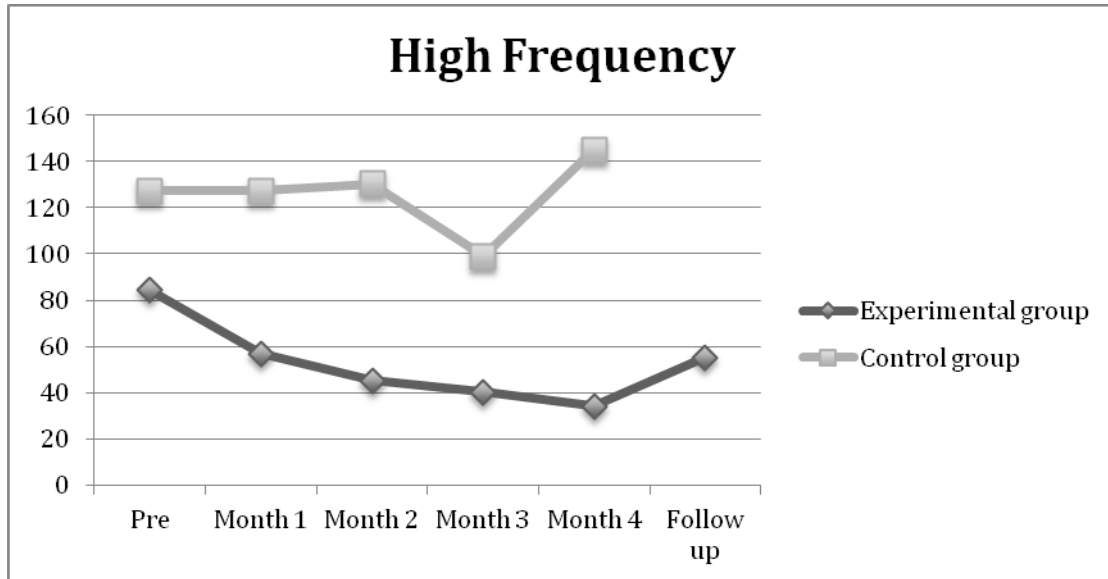
Figure 4. High Frequency throughout the Treatment/Waiting Period

The analysis of patients who responded to treatment indicated that the reduction was not statistically significant (p=0.2482) and effect size remained medium (Cohen's d=0.578).

3.8 Low Frequency

Although there was no statistically significant difference between the groups' mean LF before and after treatment/waiting period (p=0.1859), there was a score decrease in this parameter in the experimental group. The effect size was medium (Cohen's d=0 763) (Figure 5).

Figure 5. Low Frequency throughout the Treatment/Waiting Period

The analysis of the subjects who responded to the treatment shows that the reduction achieved borderline statistical significance (p=0.0833) and large effect size (Cohen's d=2.097).

3.9 RMSSD

Regarding RMSSD, there was no statistically significant difference between the mean score of the groups before and after treatment/waiting period (p=0.2568). The effect size was small (Cohen's d=0.207). In the experimental group, this parasympathetic index remained decreased during treatment and increased further in the follow up period (Figure 6).
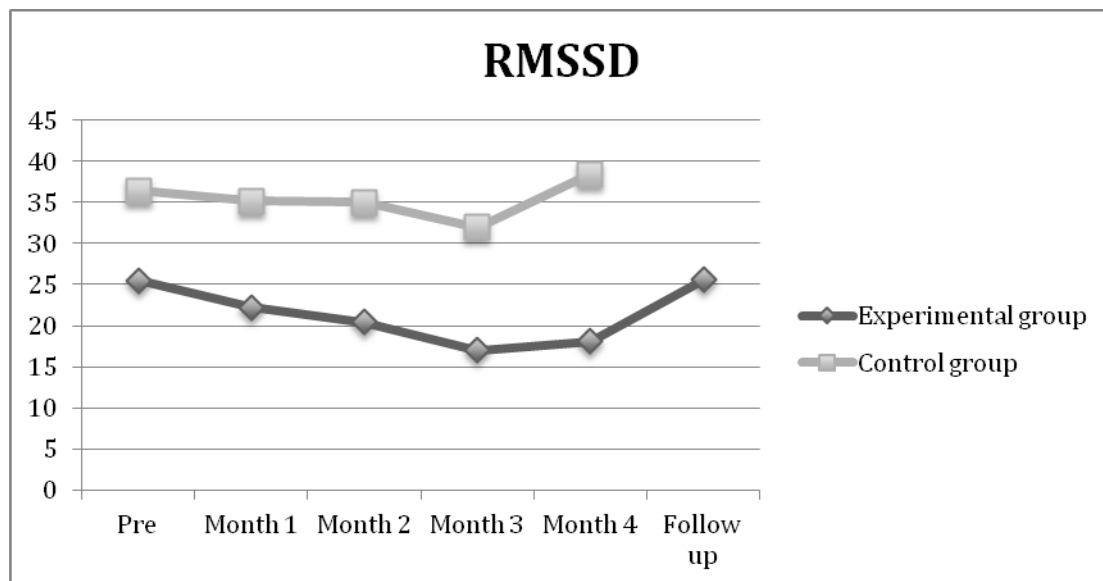
Figure 6. RMSSD throughout the Treatment/Waiting Period

The analysis of the subjects who responded to the treatment indicates no statistically significant difference when compared to the control group (p=0.2482). The effect size remained small (Cohen's d=0.323).

3.10 Endocrine Variable

Salivary cortisol samples of five subjects in the experimental group and four in the control group were analyzed. Three samples were lost due a storage procedure error. The comparison between the average group scores before and after treatment/waiting period indicates no significant difference (p=0.4561). The effect size was medium (Cohen's d=0.638).

In the experimental group, cortisol slightly dropped in month 1, increased in month 2, decreased again towards month 4 and remained lower in the follow up. Cortisol level decreased 1.2 nmol/L between the first and last evaluation (Figure 7).
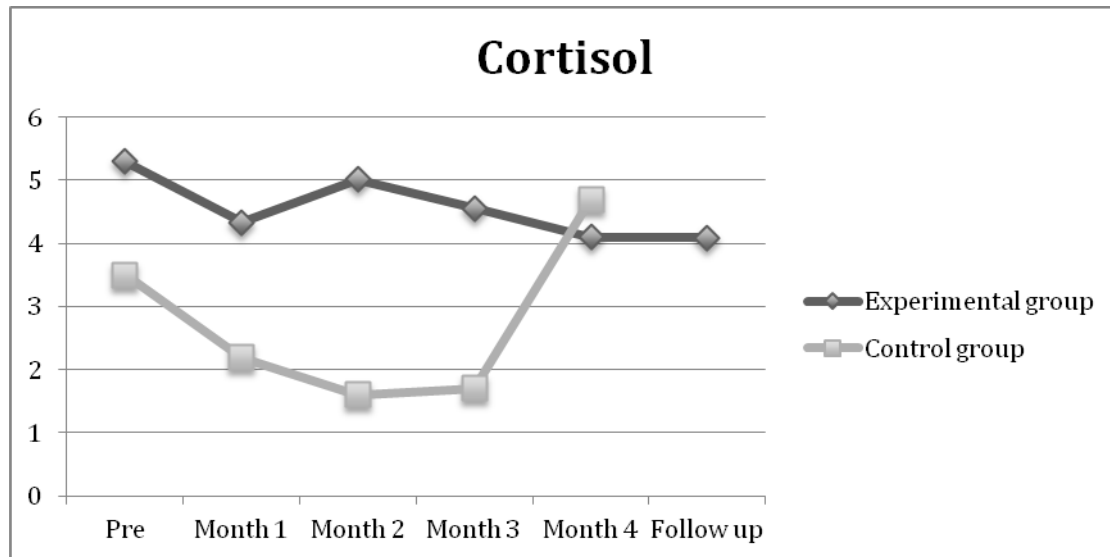
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Figure 7. Cortisol Level throughout the Treatment/Waiting Period

The analysis of the treatment responders indicates no statistically significant difference between groups (p=0.4795). Effect size remained medium (Cohen's d=0.575).

4. Discussion

This study differs from the existing literature in two aspects: this is the first randomized controlled trial that evaluates psychometric, cardiac and endocrine parameters at rest in patients with PTSD. The measurement of biological parameters is usually performed during symptom evocation and, when at rest, it is done before symptom evocation (Dunne et al., 2012; Hinton et al., 2009; Fecteau & Nicki 1999; Sloan et al., 2011). This study is also a pioneer in the evaluation of these parameters throughout the therapeutic process. As far as we are aware, previous studies involving PTSD evaluated the heart rate or cortisol only before and after CBT treatment (Gonçalves et al., 2015; Gerardi et al., 2010; Smyth et al., 2008).

4.1 Psychometric Parameters

The results of this pilot study suggest a reduction of PTSD symptoms in patients treated with a CBT protocol. Although there was no statistically significance difference between groups (p=0.5676) according to PCL-C, probably due to the low sample power, the effect size was large (Cohen's d=0.859). Furthermore, a reduction of 18.5 points observed in the treatment responders is considered clinically significant. This result is in accordance with the literature that shows the efficacy of CBT in the treatment of PTSD in a wide range of studies (Bisson, 2007; National Collaborating Centre for Mental Health, 2005). Furthermore, there is a linear decrease of the PTSD symptoms from month 1 to month 4, which is indicative of fast and consistent therapeutic benefit, even when anxiety during the early stages of the exposure technique is present.

4.2 Neuroendocrine Parameters

Regarding cortisol, although there was no statistically significant difference between groups (p=0.4561), levels of this hormone tended to follow the treatment, in that it decreased during psychoeducation, anxiety management and cognitive restructuring periods (month 1), increased during the early period of the exposure technique (month 2), decreased by the end of treatment (from month 3) and remained lower in the follow up. Cortisol peak may have been influenced by the exposure technique, the most efficacious technique in the treatment of PTSD. It might indicate that engagement in the treatment, which can initially increase anxiety, is important for the future decrease in cortisol level and subsequent improvement of symptoms. This finding is consistent with the increase in the activation of brain areas that initiate HPA axis activity via connection with the hypothalamus during the exposure period (Gottfried & Dolan, 2004; Knight et al., 2004). Increased anxiety in the early stage of treatment could have an impact on brain structures that release stress related hormones, which would be regularized by the time habituation occurs.

In addition, the decrease in cortisol levels after treatment, which obtained medium effect size both when analyzing the total experimental sample (Cohen's d=0.638) and only treatment responders (Cohen's d=0.575), is consistent with the reduction of PTSD symptoms observed in PCL-C. The literature suggests that the levels of this hormone, when measured at rest and in the afternoon, are higher in patients with PTSD comorbid with major depression when compared to subjects who suffered trauma and did not develop PTSD (Morris et al., 2012). In this respect, the results confirm that the cortisol decrease caused by CBT seems to regularize previously increased levels of this hormone.

4.3 Cardiac Parameters

In respect of the cardiac parameters, although the literature suggests that PTSD patients have increased baseline heart rate and decreased heart rate variability when compared to subjects who have undergone trauma but did not develop PTSD (Buckley & Kaloupek, 2001; Pole, 2007; Norte et al., 2013), there are no studies measuring the impact of CBT on these parameters at rest. It was expected that heart rate would decrease in month 4 (end of treatment), but we observed this only in the follow up period. In the control group, this parameter remained stable, and there was an increase from the beginning to the end of the waiting period, following the PCL-C. Regarding the parasympathetic components of heart rate variability, contrary to what was expected; there was a reduction in both the HF and the RMSSD at the end of treatment. The HF followed the PCL-C during treatment, decreasing along with the decrease of symptoms, whereas the initial hypothesis was that it would increase. Regarding RMSSD, although there was a decrease in the last assessment, in the experimental group this parameter remained low throughout the treatment, which is consistent with the increased anxiety during the exposure technique. In the control group, as expected, this index remained more stable. We can therefore say that in the resting state, an increase in parasympathetic activity caused by CBT was not detected.

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With respect to the LF, a predominantly sympathetic index, the hypothesis that it would be reduced by the end of treatment was confirmed. In addition, in the experimental group this parameter followed the decrease in the PCL-C up to month 3 and again at follow up. In the control group, there was an increase in LF at the end of the waiting period, which is also consistent with the psychometric variable. The analysis with treatment responders showed a borderline statistical significance (p=0.0833) and the effect size increased from medium to large (Cohen's d=2.097). Given the sample size of this pilot study, we must be cautious in generalizing this result. However, replication of this finding would confirm the reduced activation of the sympathetic nervous system caused by CBT. The impact observed on this index possibly reflects the reduction of symptoms of hyperarousal observed in PTSD.

It is possible that the parameters measured in this study would have followed the stages of treatment if they had been measured during symptoms evocation. This study has given us the opportunity to observe that in the resting state, this response does not occur in all parameters. Cortisol levels, even though measured at rest, rose and fell as expected throughout the therapeutic process. A larger sample size would possibly produce greater statistical significance to the results which at present only point in this direction.

Identifying CBT's biological mechanisms of action may encourage the creation and improvement of techniques that are effective in modifying pathological biobehavioral manifestations. As a result, it will expand the ability to personalize treatment, taking into account different subtypes of the disorder, and reducing the therapeutic time required to overcome maladaptive behaviors.

5. Limitations

The main limitation of this study is the small sample size, which increases the risk of type 2 error. Another limitation concerns the use of pharmacological treatments during the protocol/waiting period and the absence of a blind evaluator. In addition, we did not use the original and most widely-used questionnaire for the evaluation of symptoms, the Clinician Administered PTSD Scale (CAPS).

6. Conclusions

The results of this pilot study showed no changes in cardiac and endocrine parameters caused by CBT, when measured in a resting state. However, this is a pilot study with a small sample, which leads to the possibility of false-negative results. In regard to neurobiological parameters, cortisol levels tended to parallel the therapeutic process, rising during the early period of exposure and decreasing in the psychoeducation, anxiety management and cognitive restructuring phases. CBT impact was observed in the LF index of heart rate variability, which may be related to the reduction of autonomic arousal symptoms caused by CBT. The other cardiovascular parameters, on the other hand, when measured in a resting state, did not follow the impact of CBT, suggesting that only cardiac reactivity measured during symptom evocation responds to the impact caused by the treatment, or that the sample was too small to

achieve statistical significance.

Compliance with Ethical Standards

Conflict of Interest: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. All the authors declare that we have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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