

Research Article

Effect of Caffeine Intake in Vestibular Function: A Randomized, Triple-Blind, Controlled Trial

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Abstract

Objective: To assess the effect of caffeine in the following vestibular function tests: Cervical Vestibular Evoked Potential (cVEMP), Ocular Vestibular Evoked Potential (oVEMP) and Caloric Test.

Methods: Randomized, prospective triple-blind, placebo controlled clinical trial. All participants underwent otoscopy, tympanometry and responded to the Profile of Mood State (POMS). They were submitted to the cVEMP, oVEMP and caloric tests. After that they received placebo capsule (maize starch) or caffeine capsule (300mg) and repeated the procedures 45 minutes later.

Results: There were no statistically significant differences in latencies, peak to peak amplitudes, asymmetry ratio or rate of change in cVEMP. A statistically significant difference was observed in the caffeine group ($p < 0.05$ latency of left ear) in oVEMP. The Non-caffeine group showed statistically significant difference between the relative values in caloric test. No variable of any test was influenced by caffeine intake.

Conclusions: Moderate caffeine consumption does not significantly alter vestibular function tests.

Significance: This study provides the evidence that cVEMP, oVEMP and caloric test do not suffer influence from moderate caffeine consumption.

INTRODUCTION

In vertigo patients vestibular tests are indicated in order to identify the presence of changes and find the affected area. Thus a thorough investigation of the peripheral and central vestibular organs is required [1,2].

Caloric test is an important tool in vestibular evaluations and it investigates the horizontal semicircular canals [3,4]. The application of different temperatures to the external auditory canal (warm or cold) generates an endolymphatic movement inducing the appearance of nystagmus [5]. Cervical vestibular evoked myogenic potentials (cVEMP) is a manifestation of the vestibulo-colic reflex [6-8]. It is an inhibitory electromyographic potential, due to acoustic stimuli of high intensity, which excites the saccule and inferior vestibular nerve (sacculocollic pathway). Since the first description it has become a well-established clinical test of vestibular function [9].

Ocular vestibular evoked myogenic potentials (oVEMP) reflect predominantly utricular -otolith function and crossed vestibulo-ocular pathway - superior division of the vestibular nerve [10-12]. The response consists of a series of waves, beginning with a negative peak followed by a positive one [13].

The posterior labyrinth is a highly sensitive organ to changes in other organs and systems, so many of these changes first manifest with vestibular symptoms [14].

Caffeine is a psychoactive substance very commonly used in the world, found in the most diverse products such as food and drugs. Being a stimulant of the CNS it is believed that it excites the labyrinth, but no strong scientific evidence of this relationship exists [15-18]. While there is no consensus on this interaction, each service adopts recommendations that seem convenient, making it difficult to compare the exams. In addition, patients are subjected to a strict diet that can have systemic effects on habitual caffeine users, such as severe headaches, making it difficult to cooperate during the tests.

The aim of this study is to assess the effect of caffeine in the following vestibular tests: cVEMP, oVEMP and caloric test.

MATERIALS AND METHODS

Study design

This is a randomized, prospective triple-blind, placebo controlled clinical trial approved by the institutional review board under protocol number 1.399.322/16 and registered in Clinical Trial. Informed consent was obtained after a full explanation of the experimental procedure.

Eligibility

The sample was made up of medical students who agreed to participate as volunteers and had no hearing and/or vestibular complaints or other health problems that could affect the homeostasis of the vestibular system (problems in the cervical spine, cardiovascular problems, migraine, metabolic disorders, hormonal changes, psychiatric disorders, neurological diseases, use of prescription drugs continuously, were smokers, alcoholics, or illegal drug users). It consisted of 32 healthy young subjects randomly divided into two parallel groups: caffeine [18] and non-caffeine [14], similar to each other in terms of age and daily caffeine intake (Figure 1).

Randomization and allocation concealment

At baseline, study participants were randomized to receive caffeine or placebo at a 1:1 ratio, by independent statistician. We used a completely randomized design for two treatments with

PLAN procedure (SAS 9.4). The allocation was made for a collaborator, who identified the capsules in identical packages labeled with the name of the participants. The active (300mg caffeine) and placebo (maize starch) capsules were identical in color, size, weight, and packaging.

Blinding

The collaborator responsible for labeling the capsules with the names of the participants had no contact with them, the audiologist, or the statistician responsible for the data analysis. Thus, the participants were not aware of what was contained in the capsule, as well as the audiologist responsible for collecting and analyzing the exams and questionnaires. The statistician was independent and was also unaware of the substance to which the two groups had been exposed.

Intervention

Subjects were invited to participate in the study through telephone contact and were advised to abstain from products that contained caffeine 24 hours before their participation. The same detailed guidelines were sent by email. All participants were questioned about compliance with the recommendations for the exams and those who declared they had not followed, however, still wished to participate in the study, had their exams re-scheduled.

All participants underwent otoscopy and tympanometry, responded the Profile of Mood State (POMS), and were submitted to the cVEMP, oVEMP and caloric tests in that order. After that

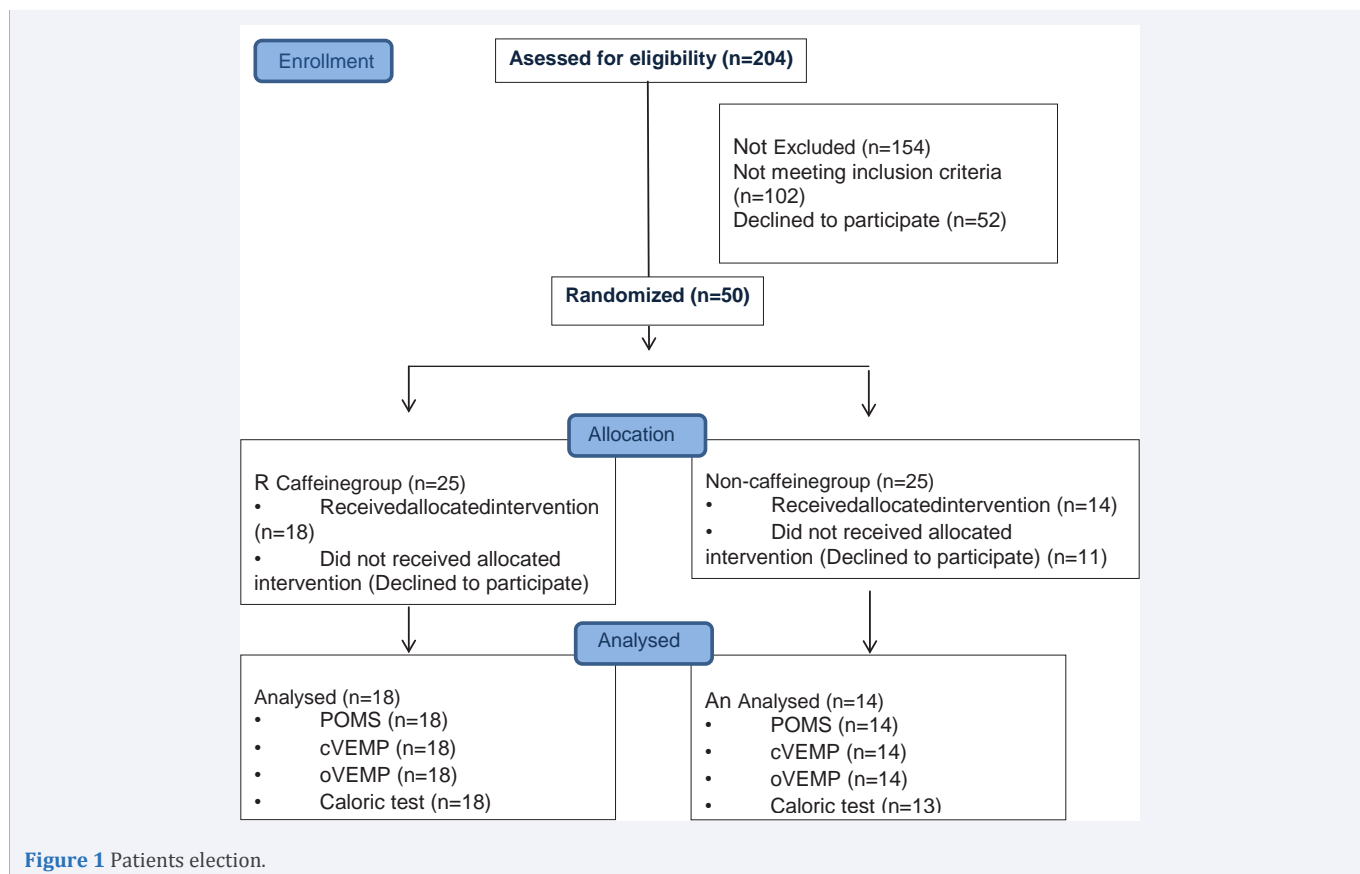


Figure 1 Patients election.

they received placebo or caffeine capsule. After 45 minutes they again responded to the POMS, repeated the cVEMP, oVEMP and caloric test. The procedures were repeated 45 minutes after ingestion of the capsule because it corresponds to the peak plasma concentration of caffeine [19]. The tests were performed in a center for rehabilitation of hearing and balance by the same audiologist. Data collection time was 3 months.

Caffeine consumption

To determine caffeine consumption a questionnaire which sought to investigate eating habits was applied. They have to include for each item (coffee, teas, soft drinks, chocolate, powdered chocolate, powdered guarana, food supplements and energy drink) the amount, kind (i.e. espresso, filter coffee) and brand. Based on these data, the consumption was calculated using a pre-validated standardization [20]. Those who had higher intakes equal to 500mg / day or more (heavy or very heavy) were excluded.

POMS

The questionnaire was developed with the objective of investigating mood states and their fluctuations in psychiatric patients and in normal adults, becoming a widely used tool in caffeine research [21].

Self-administered instrument that consists of 65 items describing feelings; to them values should be assigned from 0 to 4 according to the Likert scale of 5 points (0 - no, 1 - a little, 2 - more or less, 3 - well, 4 - extremely). The POMS aims to evaluate six factors: tension-anxiety (9 items), depression-dejection (15 items), anger-hostility (12 items), vigor-activity (8 items), fatigue-inertia (7 items), confusion-bewilderment (7 items), and a total mood disturbance score (TMD) [22].

cVEMP

VEMP was performed in response to air-conducted stimuli, using alternate 500Hz tone bursts presented at 120 dB pSPL and rate of 5.1 stimuli per second [23]. Band pass filter of 10 Hz to 1500 Hz was used, 50ms window and 200 stimulations in each track were standard. Two stimulations were recorded on each side, in order to observe the replicability [24]. The stimuli were presented via insert earphones ER-3A.

A cleaning of the skin with abrasive paste was performed and surface electrodes were affixed using conductive paste. The non inverting electrode was placed in the middle part of the sternocleidomastoid [25], the ground electrode in lower forehead and the inverting on the upper forehead. The impedance of the electrodes should be less than or equal to 5hms. Subjects were positioned seated and instructed to maintain maximum head turn to the side contra lateral to the stimulus throughout stimulation [26].

The latency of p13 and n23 and the amplitude peak to peak were analyzed in each ear and an asymmetry rate was also analyzed. For the last one we used the formula $\frac{\text{amplitude of right ear} - \text{amplitude of left ear}}{\text{amplitude of right ear} + \text{amplitude of left ear}} \times 100$ [27]. To compare the amplitudes in each ear before and after tests we used the rate of change formula, consisting of $\frac{\text{amplitude of ear before} - \text{amplitude of ear after}}{\text{amplitude of ear before} + \text{amplitude of ear after}} \times 100$ [28].

We considered normal p13 latencies between 13.9 to 19.2 and from 22.9 to 30.3 n23 latencies [29] and the asymmetry rate and rate of change of up to 28% [28].

oVEMP

We used the same parameters of stimulation and analysis described in cVEMPs as previously proposed [8]. Non inverting electrodes were placed on the face just inferior to each eye (inferior oblique muscle), reference electrode was placed 1-2cm below contra lateral to the stimulus and ground electrode in the forehead. The subject was placed in the sitting position and instructed to look upward [8,9]. The latencies of initial negative (n1) and positive (p1) peak were measured. We considered normal n1 latencies from 10.2 to 11.8 and from 14.7 to 17.3 p1 latencies [9].

Caloric test

To perform the caloric test we used an air oto calorimeter, and carried out four stimulations of 60 seconds each, with a flow of 8 liters per minute: 50°C in the right ear, 50°C on the left, 24°C on the left ear and 24°C in the right ear, in this order. The absolute values and percentages of unilateral weakness or directional preponderance were analyzed for each subject in each test. They were considered normal when they showed absolute values from 3 to 45°, a range of 30% or less in directional preponderance and of less than 25% in the unilateral weakness [1].

Outcomes

The primary outcome was the latency of waves for cVEMP and oVEMP and absolute and relative values for caloric tests. These parameters were chosen for analysis of the primary outcome for being the most well-established parameters for use in clinical practice. The secondary outcomes were asymmetry ratio and ratio of change for cVEMP. There were no secondary outcomes for oVEMP and Caloric test.

Statistical analysis

Non-parametric tests were used seeking statistically describe and compare the two groups - caffeine and no caffeine (Mann-Whitney test), the two time points - before then within each group (Wilcoxon signed-rank test) and study the statistical effect of caffeine consumption on the other variables (Jonckheere-Terpstra test). ACI of 95% was used.

The spread sheet MS-Excel was used in the version of MS-Office 2013 for the organization of data, and IBM SPSS (Statistical Package for Social Sciences), in its version 23.0, to obtain the results.

RESULTS AND DISCUSSION

The sample was composed of 27 females and 5 males ranging in age from 18 to 42 years (mean: 26,88 ±SD:6,98 yr). Subjects reported consuming an average of 65,63mg/day (SD: 68,33) of caffeine. The distribution of the groups is shown in Figure (2). The choice by young individuals occurred to exclude degenerative processes of vestibular system structures that occurs at advanced age as a part of the multiple sensorial loss of aged individuals [30].

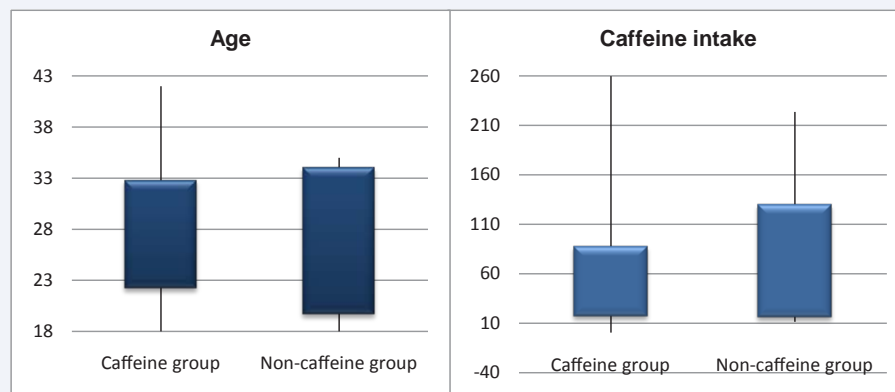


Figure 2 Distribution of sample according to age and caffeine intake.

In the literature we found few studies that estimated the intake of caffeine: most estimated the coffee intake. In this study the average consumption of caffeine was 65,63mg / day, consumption much lower than reported by other studies [31-33]. The low habitual caffeine consumption reported by the participants would make us to believe that they would suffer more the effects of abrupt consumption of moderate dose of caffeine.

The groups showed no statistically significant difference either in POMS or TMD comparing caffeine and non-caffeine. Comparing the two periods, there was statistically significant improvement in depression-dejection and anger-hostility in the caffeine group and in tension-anxiety, anger-hostility and confusion-bewilderment in the placebo group see Table (1). Decrease in depression-dejection was reported in another study [33]. However, the results disagree with the majority of studies that found increase in vigor-activity [17,34-37] and reduction in fatigue-inertia [34,36,38] after caffeine intake. This fact is attributed to the low consumption of caffeine in the habitual diet of the participants.

Regarding the caffeine intake we found a strong relationship between consumption and the TMD: the higher the caffeine intake the greater was the change in mood, a fact previously reported [39]. Evidenced by the Jonckheere-Terpstra test with p-value of 0.022.

In cVEMP, there were no statistically significant differences in latencies (p13 and n23), peak to peak amplitudes, asymmetry ratio or rate of change between the caffeine and non-caffeine groups. Comparing the two moments (before and after the capsule) there was also no statistically significant difference in any of the parameters analyzed. This was also observed in other studies investigating the action of caffeine in healthy individuals [28,40].

With respect to oVEMP, there were no statistically significant differences in latencies (n10 and p15) between the caffeine and non-caffeine groups. Comparing the two moments a statistically significant difference was observed in p15 latency of left ear in the caffeine group. This finding did not affect the clinical outcome of this test. We did not find other study that tried to analyze the effect of caffeine on oVEMP.

Considerable research efforts have led to better understanding oVEMP. In the last years, they focus primarily on determining the origin of responses, standardization of the stimulus, electrode placement and position of the patient [13,41]. We did not find studies suggesting some preparation for the exam: diet, medication usage restrictions, etc [9,12]. This demonstrates the need for future studies. Other analyzed parameters did not show this difference (Table 2).

In caloric tests one of the non-caffeine group participants presented neurovegetative exacerbated symptoms during the first examination, and was not submitted to the second test. As a consequence the caloric test statistical analysis was performed with 31 participants: caffeine group (18) and non-caffeine group (13).

In caloric tests the averages of the Peak slow velocity (PSV) in all stimulations were similar in both groups. Likewise, in the caffeine group all stimulations were statistically similar comparing the before and after caffeine intake. All participants had the same type of analysis (unilateral weakness or directional preponderance) in the two moments. In this group, one of the participants presented hyper reflexia during the warm and cool stimulation of the left ear at both times. The results were similar to those found previously [40,41].

The non-caffeine group showed statistically significant difference between the relative values before and after capsule intake (Table 3). It can be noted that all participants got the same report in the tests performed before and after placebo capsule, showing that the differences were of no clinical value. These differences can be explained by the low test-re-test reliability of the caloric test [32]. It is important to point out that variance for calorics is large and is dependent on several factors, such as attention, the effectiveness of caloric stimulation, and size of ear canal [40].

No variable of any test (cVEMP, oVEMP, caloric test) was influenced by caffeine intake, showing that habitual caffeine consumption had little effect on the parameters analyzed in these tests.

CONCLUSION

Moderate caffeine consumption does not significantly alter the clinical interpretation of the results obtained in the vestibular

Table 1: Comparing the values before and after capsule intake in the Profile of Mood State in each group.

	Caffeinegroup				Non caffeinegroup			
	n	Mean	SD	P value	n	Mean	SD	P value
Total Mood Disturbance before	18	2,56	23,14	0,170	14	6,93	26,84	0,079
Total Mood Disturbance after	18	-2,33	16,42		14	-3,50	16,79	
Tension-anxiety before	18	4,28	5,29	0,138	14	5,57	4,74	0,019
Tension-anxiety after	18	3,00	4,83		14	1,64	4,27	
Depression-dejection before	18	4,00	6,27	0,003	14	3,64	5,98	0,082
Depression-dejection after	18	1,28	2,80		14	1,71	2,49	
Anger-hostility before	18	2,11	3,58	0,015	14	4,07	6,08	0,028
Anger-hostility after	18	0,39	0,85		14	1,57	3,72	
Fatigue-inertia before	18	6,50	4,05	0,154	14	7,29	6,50	0,084
Fatigue-inertia after	18	5,50	4,49		14	4,86	4,15	
Vigor-activity before	18	16,22	6,92	0,568	14	16,29	4,65	0,556
Vigor-activity after	18	16,61	8,02		14	14,86	6,84	
Confusion-bewilderment before	18	1,83	4,48	0,296	14	2,93	5,54	0,018
Confusion-bewilderment after	18	0,94	3,99		14	-0,21	2,05	

Table 2: Comparison of before and after capsule intake in the caffeine and non caffeine groups in oVEMP and cVEMP parameters.

		Caffeine group			Non caffeine group		
		Before	After	P value	Before	After	P value
oVEMP Latency Mean (SD)	n1 Right ear	11,04 (0,50)	11,07 (0,43)	0,850	11,01 (0,51)	11,10 (0,48)	0,187
	n1 Left ear	11,2 (0,49)	11,21 (0,43)	0,717	11,06 (0,38)	11,05 (0,47)	0,730
	p1 Right ear	15,89 (0,79)	15,75 (0,77)	0,275	15,63 (0,77)	15,80 (0,73)	0,148
	p1 Left ear	15,65 (0,56)	15,93 (0,52)	0,025	16,04 (0,86)	15,91 (0,54)	0,397
cVEMP	p13 Right ear	17,35 (1,79)	17,18 (1,61)	0,348	16,56 (0,99)	16,76 (1,20)	0,107
	P13 Left ear	17,07 (2,13)	17,30 (1,93)	0,072	16,50 (1,53)	16,56 (1,67)	0,386
	n23 Right ear	25,37 (1,95)	25,40 (1,93)	0,831	24,05 (1,66)	24,45 (1,83)	0,184
	n23 Left ear	25,42 (2,82)	25,43 (2,97)	0,571	24,35 (2,09)	24,45 (2,28)	0,550
Amplitude	PPA Right ear	90,39 (54,28)	77,53 (38,19)	0,133	72,90 (42,06)	89,14 (38,72)	0,084
	PPA Left ear	92,24 (47,88)	82,93 (47,63)	0,071	79,04 (45,07)	79,37 (32,34)	0,975
	Asymmetry ratio	14,03 (7,13)	11,05 (8,71)	0,286	15,60 (9,69)	9,92 (9,49)	0,221
	RC Right	17,64 (18,40)			0,744	20,66 (16,54)	
RC Left	17,10 (15,78)			21,09 (15,27)			

Table 3: Comparison of before and after the caffeine group and non caffeine regarding Caloric test parameters: PSV for each irrigation, percentage of unilateral weakness or directional preponderance.

	Caffeine group			Non caffeine group			Total	
	Before	After	P value	Before	After	P value	P value before	P value after
RE warm	15,78 (8,52)	13,67 (9,03)	0,095	16,00 (9,30)	15,85 (8,73)	0,665	0,939	0,446
LE warm	20,72 (13,26)	19,33 (12,25)	0,092	18,50 (10,51)	17,23 (10,23)	0,125	0,790	0,748
RE cool	14,28 (11,70)	14,78 (11,06)	0,962	16,57 (9,37)	14,26 (10,08)	0,041	0,238	0,904
LE cool	15,50 (11,04)	15,78 (11,08)	0,639	15,71 (6,92)	13,23 (6,89)	0,020	0,661	0,547
DP (%)	17,71 (8,54)	23,14 (5,27)	0,063	7,50 (4,46)	18,33 (6,53)	0,027	0,044	0,223
UW (%)	19,55 (6,56)	19,18 (7,56)	0,878	22,50 (13,46)	12,14 (7,80)	0,041	0,804	0,102

Abbreviations: RE: Right Ear; LE: Left Ear; DP: Directional Preponderance; UW: Unilateral Weakness

tests: cVEMP, VEMP and caloric test. This way we can infer that it is possible to perform vestibular exams following the usual patterns of caffeine consumption in young individuals.

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