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RESEARCH ARTICLE

Effects of caffeine on cervical vestibular evoked myogenic potential: a pilot study

ElhamTavanai[1], Saeid Farahani[1], Mansoureh Adel Ghahraman[1*], Shohreh Jalaie[2], Leila Kouti[3], Farzad Shidfar[4]

[1]- Department of Audiology, School of Rehabilitation, Tehran University of Medical Sciences, Iran

[2]- Biostatistics, School of Rehabilitation, Tehran University of Medical Sciences, Iran

[3]- Department of Clinical Pharmacy, School of Pharmacy, Jondishapur University of Medicine, Ahvaz, Iran

[4]- Department of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences, Iran

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Abstract

Background and Aim: Caffeine at low doses blocks adenosine receptors. These receptors are present in all parts of the body including auditory and vestibular system. This study aimed to evaluate the effects of caffeine on cervical vestibular evoked myogenic potential (cVEMP).

Methods: In this interventional double-blind study, 40 cases (20 females and 20 males) aged 18-25 years were randomly assigned into two groups: the test group, 3 mg/kg caffeine and little sugar and dry milk in 100ml water, and the control group, placebo including sugar and dry milk in 100ml water. Myogenic potential was recorded before and after intervention with 500 Hz tone burst in 95 dBnHL.

Results: The statistical analysis revealed that there was no significant difference in p13 and n23 latency and amplitude asymmetry. However, the mean amplitudes of right ear ($p=0.04$) and two ears ($p=0.02$) of test group indicated a significant increase after caffeine ingestion. The results showed no significant difference in caffeine group compared to the placebo group in any of parameters and ears ($p>0.05$).

Conclusions: With current study small sample size we found no effect of 3 mg/kg dose of caffeine on cervical vestibular evoked myogenic potential. Although after intervention the significant increase in the amplitude of all samples was notable, no significant difference was found between the two groups. The present study was the first research in this area, however, larger sample size and different doses of caffeine is suggested for future studies.

Keywords: Caffeine, adenosine, alutamate, cervical vestibular evoked myogenic potential

[*] **Corresponding Author:** Department of Audiology, School of Rehabilitation, Tehran University of Medical Sciences, Piche-Shemiran, Enghelab Ave., Tehran, 1148965141, Iran. Tel: +9821-77530636, E-mail: madel@sina.tums.ac.ir

Introduction

Caffeine (1, 3, 7-trimethylxanthine) is the most widely used psychoactive substance in the world and is present in various foods and beverages like coffee, tea, cola, and energy drinks [1]. The most important effect of caffeine is blocking of all adenosine receptors including A1, A2A, A2B and A3. However, caffeine has other mechanisms of action such as mobilization of intracellular calcium, inhibition of phosphodiesterases and interfering with GABA receptor. In addition, neurotransmitter

levels and functions like glutamate, serotonin, noradrenaline, acetylcholine and dopamine change secondary to the adenosine blocking [2]. Adenosine not only acts as a neurotransmitter and neuromodulator but also is a constituent of other important bioactive molecules like ATP, RNA and second messengers such as cyclic adenosine monophosphate (cAMP) [3]. In Vitro studies have shown that adenosine and its structures act in auditory [4] and vestibular systems [5].

Previous studies have evaluated caffeine effects on the organ of corti [6] and auditory evoked potentials [7-9], and showed that caffeine significantly suppressed the compound action potential of the auditory nerve (CAP) and summation potential (SP) at low intensity, and increased N1 latency at high and low intensity. Additionally, caffeine has reduced distortion product otoacoustic emissions (DPOAE) at low intensities and increased it at high intensities and the result is the shortening of the outer hair cells.

In auditory brain stem response (ABR) studies, caffeine ingestion significantly has reduced latencies of waves I[7], III, V [7,8], IV[8] and also I-V interpeak interval [7,8] and increased amplitude of wave V [8].

In upper level potentials, results from numerous studies are conflicting. Caffeine has reduced MLR and P1 latency [8], reduced P300 latency and amplitude [9] and increased P1, P2 and P3b amplitude without effect on the latency [10].

There are few studies about the effect of caffeine on the vestibular system. Studies in which caloric [11] and posturography [12] were used, no significant effects was found. Studies in which oculomotor tests were used, showed that caffeine treatment significantly reduced saccadic eye movements of smooth pursuit in schizophrenic patients [13].

Due to the effect of caffeine on the auditory evoked potentials, similarities of auditory and vestibular system and presence of adenosine in all parts of the body including vestibular system, it seems that the caffeine can also affect the vestibular system and its central pathways via different mechanisms of action. Vestibular evoked myogenic potential (VEMP) can be used to evaluate the effect of caffeine on the vestibular system. Since the caloric and oculomotor tests evaluate the other parts of the vestibular system and there is no published study about the effects of caffeine on the VEMP test, this study aims to evaluate the possible effect of caffeine on vestibular system in peripheral and central parts using cVEMP test.

Methods

The present study is a double-blind, placebo-controlled interventional study which was approved by Ethics Committee of Tehran University of Medical Sciences. The study group consisted of 40 participants (20 male, 20 female) aged 18-25 years, recruited from the School of Rehabilitation , Tehran University of Medical Sciences, Tehran, Iran.

Subjects with no history of neurologic, myogenic and balance and cervical disorders, middle and inner ear diseases, psychiatric illness, habitual smoking and drinking, and use of vestibulotoxic drugs such as gentamycin and neomycin were included. Additionally, to eliminate the effect of weight, BMI of 18.5-24.9 kg/m^2 was considered as an inclusion criteria. Moreover, subjects with low caffeine intake (<200 mg/day caffeine-containing substances equivalent to up to 3 regular cups of tea, 4 glass of cola or 2 cups of coffee drinking per day) were eligible to participate in this study.

The subjects were asked to abstain from caffeine-containing substances (tea, coffee and cola) for at least 6 hours before the test. Informed consent was obtained from all participants. To assure the health of the auditory system, subjects underwent the otoscopy (Reister, Germany), immittance audiometry (Zodiac, Madsen Corp., Denmark) and pure tone audiometry (AC40, Intracoustic Co., Denmark) examinations.

Auditory system health criteria were the normal tympanogram (static compliance within the range of 0.3-1.6, middle ear pressure in -100 ± 50 range) and present acoustic reflexes with thresholds between 70-100 HL in the immittance audiometry and AC

and BC thresholds ≤ 15 dB in the pure tone audiometry.

Initially, the cVEMP was recorded for all subjects by experimenter. Then they were randomly assigned to test and control groups. Subjects and experimenter were blind to assigning groups. Therefore, caffeine and placebo were written in some 40 similar envelopes as 3 mg/kg (caffeine) and 0 mg/kg (placebo) by a research collaborator. Three mg/kg doses of caffeine is a standard dose that has been used in several studies. Twenty envelopes for dose of 3 mg/kg, and the remaining 20 envelopes for dose of 0 mg/kg were placed in a container. Then, subjects chose one of the envelopes randomly and gave it to the collaborator without opening the envelope. Afterward, body weight of subjects were obtained using a weight scale. The collaborator measured the amount of caffeine (Human Pharmaceutical, Italy) using analyzer research scale with regard to per kilogram of body weight and dissolved it in 100 ml of water. Moreover, for making the flavor better, a little powdered milk and sugar were added. The powdered milk was also used to make the appearance of drinks of both groups similar. The used cups were disposable and non-transparent. The collaborator wrote the name of subjects and the given weight of the materials in a separate list that was out of reach of participants.

Since caffeine reaches to the highest concentration in blood plasma within 30–60 minutes post-ingestion, cVEMP test was repeated after 40 minutes. In order to eliminate the order effect, the test was started randomly once for the right ear and once for the left ear. The cVEMP was recorded (chartr ICS, GNO tometrics, USA) with 5.1 rate, 500 Hz tone burst stimuli (2-1-2 duration), insert earphone, the intensity of 95 dBnHL, bandpass 10-1500 Hz filter, 100 stimuli, 5000X gain, with the active surface electrode placing over upper one-third of the sternocleidomastoid (SCM), the reference electrode placing over the upper sternum and the ground electrode placing at the forehead. For equal contraction of muscles on both sides, feedback method was used.

All analyses were conducted using the SPSS version 17 (Chicago, Ill). The normality of the distributions was assessed with the Kolmogorov- Smirnov goodness-of-fit test. To determine the main and combined effects of caffeine and gender on the cVEMP parameters, analysis of ANOVA with repeated measures was used. Finally to compare the amount of changes between the two groups in any of the parameters, independent samples t-test was used. The significance level was set at 0.05.

Results

To examine the effect of caffeine on the cVEMP within each group, the data primarily were compared between two sessions of caffeine intake (pre *vs* post- ingestion) in either test or control group. For between-group assessment, changes in the test group were compared to that of the control group. Participants were comprised 20 normal females with mean age of 23 years and 20 normal males with mean age of 22 years.

Statistical analysis at pre-ingestion session revealed that all cVEMP parameters were homogenous in both groups and there was no significant difference between the two groups in any of cVEMP parameters ($p>0.05$). Similarly, there was no significant difference between two genders in pre-ingestion session in any of cVEMP parameters.

In comparison between pre and post-ingestion sessions using repeated-measures analysis, significant difference was not found in the parameters of p13 latency, n23 latency and asymmetric ratio in either caffeine or placebo group. The only considerable result was the p13-n23 amplitude of right ear in the test group which was significantly larger at post-ingestion session compared to pre-ingestion session ($p=0.02$, $F=6.08$). The mean of right ear's amplitude in the intervention group was 144.22±58.41 at pre-ingestion session that increased to 175.15±70.90 after 3 mg/kg caffeine ingestion (post-ingestion session).

Table 1. Mean and standard deviation of cVEMP parameters before and after caffeine ingestion in the study groups

Parameters		Caffeine group			Control group		
		Before	After	p	Before	After	p
P13 latency	Right ear	16.27 (1.09)	16.44 (0.95)	0.46	16.80 (1.66)	16.89 (1.63)	0.31
	Left ear	16.94 (1.10)	16.90 (1.09)	0.81	17.01 (2.02)	16.89 (1.63)	0.55
	Both ears	16.61 (0.84)	16.67 (0.89)	0.56	16.91 (1.69)	16.92 (1.56)	0.93
N23 latency	Right ear	24.30 (1.69)	24.49 (1.49)	0.50	24.82 (1.48)	24.97 (1.27)	0.33
	Left ear	24.79 (1.95)	25.19 (1.74)	0.16	24.95 (1.47)	24.73 (1.66)	0.73
	Both ears	24.54 (1.45)	24.84 (1.38)	0.14	24.89 (1.41)	24.85 (1.28)	0.73
Amplitude	Right ear	144.22 (58.41)	175.15 (70.90)	0.02	136.08 (79.80)	132.56 (69.03)	0.74
	Left ear	161.13 (75.12)	171.97 (62.20)	0.26	139.81 (90.40)	143.53 (113.87)	0.77
	Both ears	172.02 (103.42)	197.74 (101.27)	0.02	137.95 (78.17)	138.04 (80.83)	0.96
Asymmetrical ratio		0.03 (0.19)	-0.01 (0.20)	0.46	0.01 (0.18)	-0.008 (0.28)	0.55

Considering the mean of two ears instead of each ear independently, significant increase in the p13-n23 amplitude of intervention group was also observed (p=0.02, F=5.92).

The means and standard deviations of all cVEMP parameters are presented in Table 1 for each session and group separately.

Comparing the two groups in all subjects, they revealed no statistically significant difference in any of parameters. However, changes of the right ear amplitude approached near the significance level (p=0.06). In latencies, the latency of n23 wave was also near the significance level (p=0.08).

Similarly, considering the mean of amplitude for two ears, a significant difference was not found. Mean of changes in cVEMP parameters are depicted in Figure 1.

When we considered dose and gender as a combined variable, no interaction was found for caffeine and placebo with gender in the latencies of p13, n23 and asymmetry ratio of amplitude in none of the groups. Just for the p13-n23 amplitude, a significant interaction was found. In other word, when we consider caffeine and gender as factors, only the right ear amplitude of males showed significant difference (p=0.04, F=4.87) in test group. However unlike the amplitude of right ear, caffeine consumption did not interact with gender when we considered mean of amplitude for two ears.

When we performed between-group comparison for each gender separately, a significant difference was observed only in the right ear amplitude of males (p=0.04, F=4.60). This is similar to the within-group comparison, where just right ear amplitude of males in the test group showed significant difference after caffeine intake. In addition mean of amplitude for two ears was near the significance level just for males (p=0.09). In the other word, in test group mean of the amplitude of two ears was considerable but not significantly different from male controls.

Discussion

In general, comparison of the two session (pre *vs* post-ingestion), showed no significant difference in the latencies of p13, n23 waves

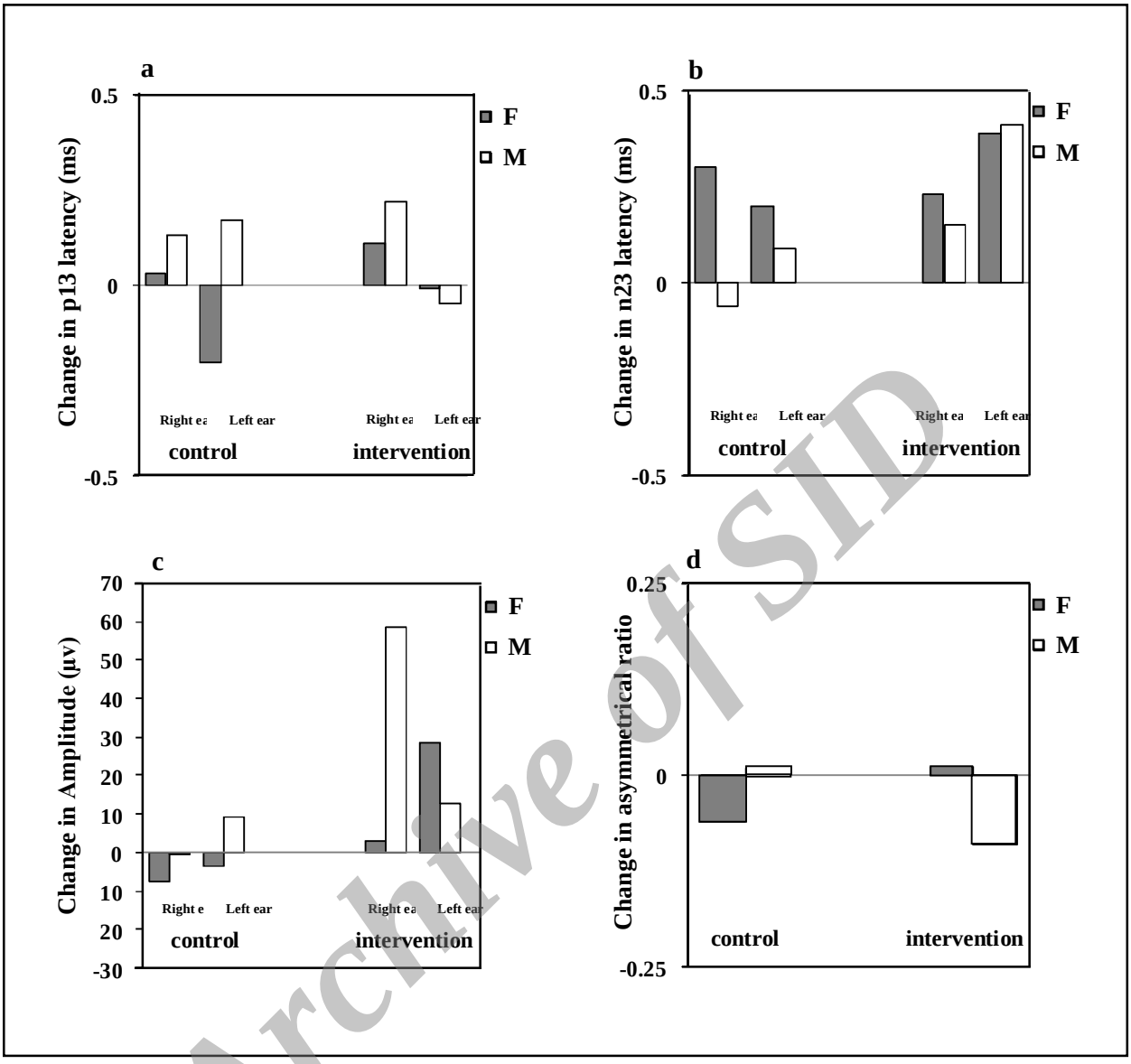

Fig. 1. Comparing of changes in mean of cVEMP parameters between two groups in the both genders: a) p13 latency, b) n23 latency, c) amplitude, and d) asymmetrical ratio.

and asymmetry ratio of amplitude. Only the amplitude of right ear and mean of amplitude of two ears showed a significant increase after caffeine ingestion compared to pre-ingestion session in the test group.

Comparison of changes between the two groups in both males and females, showed no significant difference in any of the parameters and ears. However, some of the parameters including right ear amplitude, mean of amplitude of the two ears and the latency of n23 approached to near the significance level. In addition, caffeine was associated with gender in a way that a significant increase in amplitude was observed after caffeine ingestion in males. In between-group comparison, the significant difference in the amplitude was also observed in the males' right ear.

Caffeine dose-response curve is like an inverted U and at different doses has different effects. Therefore, to explore effects of caffeine the administered dose and method of study are important. To the best of our knowledge, this study represented the first research investigating effect of caffeine using cVEMP. The significant increase in the p13-n23 amplitude following 3mg/kg caffeine ingestion in the present study is consistent with significant increase in the amplitude of wave V of ABR and amplitude of wave P1 of LLR in the study of Dixit et al (2006) who used similar dosage on 40 subjects.

In the study of Barry et al (2007) by event-related potentials (ERP), a significant increase in the amplitude of P1, P2 and P3b was observed at the dose of 250 mg on 24 subjects [10]. However, in ERP studies, other factors such as increased levels of attention and arousal are involved that they are also affected by caffeine distinctly. The cVEMP like ABR and unlike the cognitive tests doses not require the attention. Therefore, comparing the present study results with that of the ERP studies seems unreasonable. In studies using visual evoked potentials, 3 mg/kg caffeine has increased the amplitude of P2 (Ruijter et al., 1999) and n2b (Lorist,1995)[15].

According to our hypothesis in the present study, caffeine can increase amplitude of cVEMP by its effects on the neurotransmitters and blocking of adenosine receptors. Main mechanism of action of caffeine occurs at doses that block adenosine receptors. Adenosine is present in vestibular system. In addition, glutamate which is affected by caffeine, is one of the essential neurotransmitters in the vestibular and hearing system. It is possible that caffeine has increased neuronal excitability and affected evoked potentials via direct impact on adenosine or indirect impact on glutamate neurotransmitter. Extent of these effects on the various evoked potentials is presumably different. Perhaps this is because of the caffeine has complex psychophysiologic roles and the recently evidenced differences in individuals' body responses to caffeine.

Another possible reason that caffeine can increase amplitude of cVEMP is probably the effects of caffeine on the motor system [16]. Many emerged studies indicate that by increasing of the serotonin concentrations caffeine can enhance neuromuscular coordination and increase neural firing in regions of brainstem that have excitatory projections to the spinal motor neurons [17]. It is possible that caffeine has affected the SCM muscle and resulted in increasing of the cVEMP amplitude.

While examining association of gender and ear effect in the present study, we found increasing of the amplitude in the right ear of males and in the mean of two ears which was consistent with study of Dixit et al (2006). In Dixit et al. study, significant results were observed only in the mean of two ears values, and due to likely effects of hormones in males. We found no study evaluating combined effect of caffeine and gender. Although, there are studies reporting on gender differences in metabolism of caffeine. Thus, no effect of caffeine on females in the present study was probably due to the hormonal fluctuations or genetic factors. Further studies are necessary in this regard.

In Barry et al (2007) study, caffeine had no effect on P1, P2 and P3B latency that is in consistent with no change of p13 and n23 latencies in our study [10]. However significant reduction in the latency of ABR waves is reported in other studies [7, 8]. Latency of n23 showed no significant reduction in this study. Perhaps the difference between this study with ABR studies is because of the wider normal range of latency for the cVEMP than the ABR, ABR higher sensitivity to the caffeine-induced changes than the cVEMP and finally the ABR is a totally neurologic response but the cVEMP is a neurologic as well as myogenic response.

There is little information regarding the effects of caffeine on the other vestibular tests. Felipe et al (2007) study on 19 patients with vestibular disorders who were asked to abstain caffeine for 24 hours and then continue to their usual coffee drinking, showed no significant difference between the two conditions in the caloric and electronystagmography tests[11]. Also Enriquez

et al (2009) study using posturography showed no significant difference between two sessions of before and after caffeine ingestion. In study of Enriquez et al 23 young subjects stood on a platform in two conditions of open and close eyes. Then they drank two bottles of Redbull® and posturography performed again after 2 hours [12]. It should be noted that the dose of Redbull's caffeine was lower than the used dose in our study. It seems that showing caffeine-induced changes at functional level (posturography) that is expressed in unit of degrees as well as nystagmus that is expressed in unit of degree to second (deg/sec) is distinctive from showing that at neural level (cVEMP) that is expressed in unit of millisecond or millivolt and they are not comparable due to the difference in the unit. Pilli et al (2012) have reported significant reduction of saccade latency after caffeine ingestion [18]. It should be noted that used dose in this study was 500 mg that is much more than that of our study.

There are also limited reports about therapeutic uses of caffeine. Litman et al. (1989) suggested that caffeine can significantly reduce saccadic eye movements in the pursuit of schizophrenic patients [13]. It seems that such therapeutic uses are due to the positive effects of caffeine. Although this effect is in agreement with amplitude enhancement in the present study, such positive effects like cognitive tests are probably involved attention and arousal enhancement at the central nervous system. It seems that increasing of the cVEMP amplitude may have reasons other than attention and arousal enhancement.

According to the complicated roles of caffeine, its reported effects on the evoked potentials in previous studies, and significant increasing of the cVEMP amplitude in current study, we can propose that caffeine probably has an effect on cVEMP. The present discrepancies in the caffeine studies may be due to the different used doses and tests to monitor effects of the caffeine.

Conclusion

With the present study sample size, the 3 mg/kg dosage of caffeine had no effect on cVEMP. When we considered subjects altogether, the increase in the amplitude of cVEMP after the caffeine ingestion was not significant compared to the control group. However, this became significant when we analyzed each gender separately. In other words, results of males who used caffeine showed a significant increase in the amplitude of p13-n23 compared to control group males. On the other hand, absence of changes in the other important parameters like latency and asymmetry ratio may indicate that the caffeine has no significant effect on cVEMP. As our sample size was small, we can assume that those parameters that were near the significance level could be significant by increasing the sample size. To obtain more convincing results further research with larger sample size and at different doses of caffeine is recommended.

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