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Effects of Caffeine administration on GCS and GOSE in children and adolescent patients with Moderate Brain Trauma

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Abstract

Long-term consciousness impairment and mental and physical disabilities are seen in almost all patients after brain traumas of varying severities. Given the neuroprotective and stimulating properties of caffeine, the present study intended to investigate the effect of caffeine on the consciousness level and recovery rate of children and adolescent patients with moderate brain traumas (8<GCS<13). A total of 100 children and adolescent (6-17years old) patients with moderate brain trauma due to diffuse axonal injury were randomly assigned to two groups of 50. One week after trauma, in the caffeine group patients who were physiologically stable received caffeine tablets as 2.5 mg/kg/day and placebo in the second group through gavages for one month. The consciousness level and the recovery rate were assessed with GCS after one month and GOSE after six months, respectively. The two groups were similar in terms of demographic characteristics and GCS score at baseline (9.2 vs. 9.6) (p=0.581), but the mean GCS score was significantly better in the caffeine group (11.2) than the control group (9.84) after one month (p=0.024). Besides, the mean GOSE score was significantly better in the caffeine group (6.24) than the control group (4.74) after six months (p=0.036). It seems that the administration of caffeine after the acute phase of moderate brain trauma in children and adolescent patients can improve the consciousness and performance of these patients.

Keywords: caffeine, head trauma, GCS, GOSE.

Introduction

Caffeine is mainly obtained from the *Coffea arabica* plant and found in the most widely used stimulant among the general population.[1] Caffeine is easily absorbed through the small intestine[2] and reaches its peak serum level after two hours.[3] It has different effects on various organs such as the nervous and cardiovascular systems[4] which have led to various results, such as high blood pressure during resting conditions. Caffeine has strong lipophilic properties and can easily cross the blood-brain barrier (BBB).[5]

caffeine acts through inhibiting adenosine receptors in various organs, for example, adenosine acts as a neuromodulator in regulating sleep, learning, memory, and posttraumatic cell protection processes.[6]

By increasing consciousness, caffeine can improve cognitive function,[7] enhance memory,[8] and accelerate psychomotor function.[9] 150 mg of caffeine can improve cognitive function for 10 hours.[10] Numerous studies have shown the neuroprotective effect of caffeine on aging and neurological disorders through inhibiting adenosine.[11] Caffeine has an inverse relationship with the risk of Parkinson's disease[12] and Alzheimer.[13] Caffeine also has proven antioxidant effects that can protect cells at risk by preventing the peroxidation of fats.[14]

Brain trauma can occur at all ages in humans. In the United States, about 1.7 million people suffer from brain trauma each year.[15]

Brain trauma can cause sensory, physical and motor, cognitive, and behavioral problems as well as consciousness disorder, among which the latter is the most common problem after brain trauma. Also, their sensory disorders may be exacerbated and their appropriate motor responses may be reduced due to damage of structures responsible for maintaining alertness.[16] Various neurostimulator methods have been used to improve the function of the central nervous system (CNS) which yielded useful results.[17]

Numerous drugs have also been used in this field aiming to improve the cognitive status especially memory and attention of patients, including 100-300 mg/day amantadine as a dopaminergic drug in the acute and chronic phases of traumatic brain injury (TBI).[18]

Given the protective and stimulating effects of caffeine on CNS, the present study intended to evaluate the effect of caffeine on the outcome of patients with moderate brain trauma through assessing the Glasgow Coma Scale (GCS) and the Extended Glasgow Outcome Scale (GOSE).

Methods

After approval by the Research Deputy of the Kerman University of Medical Sciences, this study was carried out from the beginning of 2015 as a double-blinded clinical trial for 3 years on 100 children and adolescent (6-18 years old) patients with brain trauma who hospitalized in the intensive care unit of Sahid Bahonar Hospital in Kerman. Patients who were stable 1 week after suffering from a diffuse axonal injury due to brain trauma and had a GCS score between 9-12 were enrolled in the study after obtaining the consent of their legal guardians.

The patients were randomly assigned into two groups of 50 Patients. one group received 2.5mg/kg/day of caffeine tablets at 8 am through gavages for one month. Patients in the control group received a placebo at the same time. The other drugs used in the two groups, including analgesics, anticonvulsants, and GI prophylaxis, were matched to prevent possible interactions.

Patients with hypertension, meningitis, sepsis, organ failure, hypoxemia, history of arrhythmia or cardiac disease, history of alcohol and drug abuse, and patients with GCS <9 and >13 at baseline and diagnosis other than diffuse axonal injury were excluded. Patients who died during the study or were withdrawn from the study due to the dissatisfaction of their guardians were excluded and replaced with other qualified patients.

In both groups, the consciousness level was assessed with GCS one month after the intervention and the recovery rate with GOSE evaluation six months after brain trauma. All measurements were done by a person who was unaware of the medications prescribed.

Statistical analysis

According to a pilot study, the sample size was determined by 50 patients for each group. The descriptive data were compared using the descriptive statistics and frequency distribution, and the groups were compared using the analytical statistics and independent sample *t*-test at the significance level of >0.05 and the confidence coefficient of 95% in SPSS 20 software.

Ethical considerations

This study was approved by the ethics committee of the Kerman University of Medical Sciences with the ethics code of IR.KMU.REC.1394.453. Written consent was obtained from the patients' guardians after ensuring them of the information confidentiality, completely explaining the research process, and assuring that not participating in the study has no effect on the routine treatment.

Limitations

The limited number of eligible patients and assuring patients' guardians to participate in the study were the main limitations of this research.

Results

A total of 100 patients enrolled in the study and randomly assigned to two groups of 50. Regarding the patient's gender, 80 males (80%) and 20 females (20%) participated in the study, including 41 males and 9 females in the case group and 39 males and 11 females in the control group; there was no significant difference between the groups in this regard (p=0.870).

The mean age of the patients was 14.1±10.53years, being 13.94±10.34 years in the case group and 14.16±10.85years in the control group; there was no significant difference between the groups in terms of age (p=0.590) (Table 1).

Table 1. Demographic information of patients.

P-Value	age	sex				
		P-Value	female	male		group
0.590	14.1±10.53	0.870	20	80	total	
	13.94±10.34		9	41	case	
	14.16±10.85		11	39	control	

The patients' level of consciousness was assessed with GCS; the mean GCS score at baseline was 9.2 in the caffeine group and 9.6 in the control group, with no significant difference between them(p=0.581). However, the mean GCS score reassessed one month after the intervention was 11.2 in the caffeine group and 9.84 in the control group, indicating a significant increase in the caffeine group compared to the control group (p=0.024) (Table 2).

Table 2. Comparison of mean GCS and mean GOSE of tow groups.

P-Value	Std. Error Mean	Std. Deviation	Mean	group	group
0.581	0.25234	1.78429	9.2	case	Mean GCS one week after admission
	0.25873	1.82946	9.6	control	
0.024	0.13401	0.94761	11.2	case	Mean GCS after one month
	0.14331	1.01338	9.84	control	
0.036	0.21864	1.54603	6.24	case	Mean GOSE after six months
	0.17788	1.25779	4.74	control	

The patients' recovery rate and abilities were assessed with GOSE six months after brain trauma, which showed that the mean GOSE score was significantly higher in the caffeine group (6.24) than the control group (4.74) (p=0.036) (Table 2 and Figure 1).

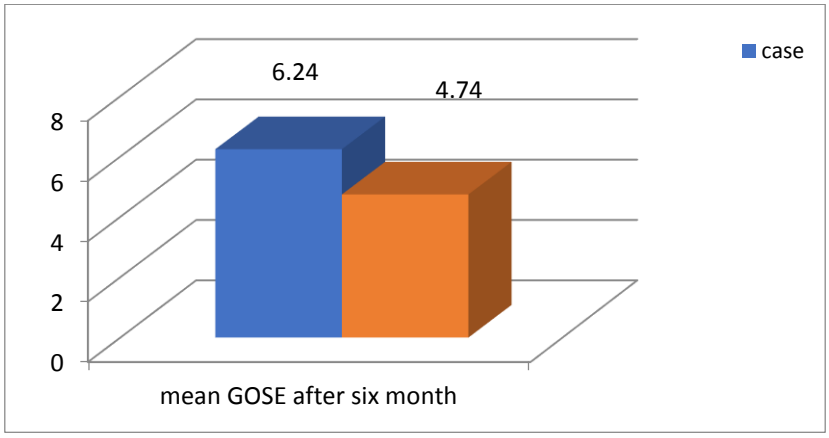

Figure 1. Comparison of men GOSE in tow groups.

Discussion

Disabilities due to brain injuries lead to economic and social problems. The most important issue in the treatment of patients with brain trauma is their quality of life after discharge. Several treatments and rehabilitation methods have been offered, such as brain stimulation methods and drugs.

caffeine is a natural brain stimulant and has several benefits. However, no study was performed so far to evaluate the effect of caffeine on the outcomes of TBI patients.

The findings of this study indicated that 2.5mg/kg/day of caffeine for up to a month can improve patients' consciousness and performance after the acute phase of moderate brain trauma in adolescent patients. Caffeine seems to stimulate the nervous system and thereby increases consciousness and concentration, improves cognitive function and memory, and accelerates the healing process of patients with brain trauma.

According to the results, there was no significant difference in the mean GCS score between the caffeine and control groups (9.2 *vs.* 9.6) at baseline (p=0.581), but after one month, the mean GCS score reached 11.2 in the caffeine group (receiving 2.5mg/kg/day oral caffeine) and 9.84 in the control group (receiving placebo), indicating a significant increase in the mean GCS score in the caffeine group compared to the control group (p=0.024).

The mean GOSE score was the other criterion assessed six months after TBI to monitor the outcome of patients. This scale objectively shows the recovery rate of TBI patients in seven categories. Although all patients benefited from the same rehabilitation program during this period, our observations showed that patients in the caffeine group had a significantly higher mean GOSE score (6.24) than the control group (4.74) (p=0.036).

methylphenidate has been used in acute TBI patients to improve attention, concentration, and memory, but these effects are not stable after three months and do not affect morbidity. However, the use of this drug in the chronic phase of TBI can improve cognitive function, especially memory and daily awakening and attention of the patient.[19] This study focused mainly on the cognitive status of patients, but the present research assessed the six-month physical activity status and GCS at the discharge time, as a reflex of the patients' consciousness level; both scales improved significantly.

Modafinil has been successfully used as a brain stimulant. It acts through increasing glutamate levels in the non-dopaminergic anterior hypothalamus, hippocampus, and amygdala in narcolepsy patients who, like TBI patients, suffer from excessive drowsiness, inattention, and inability to perform daily tasks. Teitelman E found that the administration of Modafinil in the chronic phase of TBI can reduce drowsiness and increase attention and memory.[20]

These studies, like the present research, are in favor of the use of stimulant drugs in TBI patients.

Smith A found that consumption of normal amounts of caffeine can improve behavioral status. Besides, regular consumers of caffeine had better mental performance, but high doses may result in palpitation and hypertension.[21] In the present study, caffeine improved the mental and motor function of TBI patients six months after the trauma.

Qi H showed a direct linear relationship between caffeine consumption and the prevention of Parkinson's disease so that consuming 3 cups of caffeine per day could have the highest preventive effect.[22]

Carman AJ concluded that short-term caffeine consumption is associated with improved short-term memory and cognitive function, and its long-term use prevents dementia.[23] The neuroprotective role of caffeine can be revealed from these two studies, which can be helpful in TBI patients as well. Li W *et al.* found that chronic consumption of caffeine (3 weeks before the trauma) in mice can effectively protect the trauma-induced injury, possibly through A1 receptor-mediated suppression of glutamate release and inhibition of excessive inflammatory cytokine production.[24] In another complementary study aiming to compare CSF caffeine levels in patients with severe brain trauma, Kathleen T Sachse *et al.* found that CSF caffeine levels of higher than 1 µmol/L (194 ng/mL) can protect the brain from severe traumas through long-term upregulation of adenosine A1 receptors or acute inhibition of A2a receptors,[25] which confirms the positive effects of caffeine on brain trauma.

Borota D *et al.* showed that caffeine can improve long-term memory,[26] while Nehlig A *et al.* indicated that caffeine cannot enhance pure cognition but can indirectly affect patients' cognitive status through strengthening concentration, awakening, and recovery.[27]

Caffeine is certainly effective in improving TBI patients' consciousness and performance by increasing consciousness and concentration and improving mood, which is consistent with our results.

Simone Cappelletti *et al.* found that normal amounts of caffeine can improve cognition and memory, but high doses of caffeine can be fatal, especially when taken with certain other stimulants.[28] CHS Ruxton showed that the safe effective range of caffeine in average humans is 38-400 mg/day, which increases consciousness, cognition, and physical function and relieves fatigue.[29]

As a result, caffeine should be prescribed very carefully, so that the amount of caffeine consumed was limited to 2.5mg/kg/day in this study.

According to the findings of this research and the mentioned studies, the consumption of caffeine in patients with moderate brain trauma after the acute phase can be effective in improving

patients' consciousness and performance. It is suggested to perform such a study on larger sample size and in patients with severe brain traumas.

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Declarations of interest: None

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