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Effect of a Boswellia and Ginger Mixture on the Memory Dysfunction of the Mild Traumatic Brain Injury Patients: A Randomized, Double-Blind Controlled Trial

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ABSTRACT

Objective: To study a Boswellia and ginger mixture on the memory dysfunction of the mild traumatic brain injury (mTBI) patients.
Methods: Patients with mTBI were asked about memory impairment following the injury. One hundred mTBI patients were visited and assessed using an auditory-visual learning test (AVLT) questionnaire. By using random permuted blocks, patients were given the Memoral (a mixture of 360 mg of Boswellia and 36 mg of ginger) or placebo and were asked to consume it for a month. Patients were assessed one and three months afterward using the second and third steps of AVLT, respectively.
Results: One hundred patients were included in the study and divided into control and intervention groups. The mean age of the patients was 36.83±14.71, and there were no significant differences between the two groups (p=0.41). There were no statistically significant differences in the baseline scores of different AVLT parameters between the two groups. All patients had improvements in different parameters after three months. But some factors include the scores' change in total learning, retroactive interference score, forgetting rate, and net positive score were significantly higher in treatment groups at one-month and three-month follow-ups compared to the placebo group. In contrast, word span and hit parameters had the same pattern of improvement in both groups.
Conclusion: The herbal medication can have a satisfactory effect on eliminating post-mTBI memory dysfunction while having no considerable adverse effects. The effect of these components can also be sustained after a two-month timeframe. These results may assist patients to have less mental involvement.

Keywords: Traumatic brain injury; TBI; Post-concussion syndrome; Memory impairment; Boswellia; Zingiber.

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Introduction

Traumatic brain injury is an inevitable phenomenon among different societies. Patients who have an unconsciousness duration fewer than thirty minutes and a Glasgow coma score of more than 13 are known as mild traumatic brain injury (mTBI) [1, 2]. mTBI represents up to 85% of all TBI cases and usually does not necessitate surgical interventions or prolonged hospital stays [3].

However, a group of symptoms like headache, amnesia, mood fluctuation, etc., can be expected following mTBI, which are labeled as post-concussion syndrome (PCS) [4]. In most cases, PCS symptoms would be eliminated within a few weeks without any intervention, but sometimes they may turn into chronic issues [5].

Memory disturbance after mTBI is a bothering issue that affects the life and mental health of the patients. Trauma-induced inflammation and injuries to circuits involved in memory are some of the mentioned underlying causes [5-7]. Therefore, different centers have tried to find a solution for the earlier resolution of this issue over the years [8].

Herbal medicines are accounted as a tradition among different societies, and in recent years, there have been numerous studies reflecting the efficacy of these remedies for different pathological situations. Boswellia and Ginger are accounted as two herbs that were believed to affect memory and intelligence since the old time [9, 10]. Their anti-inflammatory effects and impact on neural circuits involved in memory have been documented in different reports.

In this Randomized, double-blind, placebo-controlled, parallel-arm trial, we aim to quantitatively assess the effect of the herbal medicine Memoral on the memory function of patients who had subjective memory disruption after mTBI.

Material and Methods

Study Design

The current study is a single-center, randomized, placebo-controlled, double blind, parallel-group trial conducted in Rajaee Hospital, a tertiary referral trauma center affiliated with Shiraz University of Medical Sciences, between March and September 2022.

The trial received approval from the Shiraz University of Medical Sciences Ethics Committee with the ethics code of IR.SUMS.REC.1400.756 and has been also registered in the Iranian Registry of Clinical Trials with the registry number IRCT20130310012776N8. In accordance with the Declaration of Helsinki, and Consolidated Standards of Reporting Trials statement

(CONSORT), all participants signed written informed consent forms prior to participating in the study.

Patients' Selection

Patients who had a loss of consciousness fewer than 30 minutes, altered consciousness of fewer than 24 hours, or post-traumatic amnesia less than one day (diagnosed as mTBI) were considered for this study. Patients who admitted to the emergency room and diagnosed with mTBI and had a subjective complaint of memory dysfunction in the first follow-up session after the hospitalization (held after a week) were included in the current study.

The cases who had the following characteristics were excluded from the study: 1) age out of the range of 20 to 60 years, 2) education less than six grades, 3) a previous history of head trauma, 4) a previous history of neurologic or psychiatric disorder, 5) a major injury to other organs as a consequence of trauma 6) a history of a hematologic disorder or consumption of anticoagulant agents (due to probable adverse effects of medication components on patients with such medical backgrounds)

Sample Size

Using MedCalc (version 19.4, MedCalc Software, Ostend, Belgium), considering the α of 0.05 and the power of 80%, and the effect size of 0.6, the number of participants was determined to be 45 patients in each group (calculated using the T statistic and non-centrality parameter). As we expected a drop rate of 10%, we considered the sample size of 50 for each group.

Initially, 108 patients with complaints of memory disturbance following mTBI were assessed to know whether they meet our inclusion/exclusion criteria and have the willingness to participate. Therefore, 100 patients were found to be eligible to be included in the current study. During the follow-up of three months, 3 patients from the intervention group (those who received Memoral) and 4 patients from the control group. Figure 1 shows the process of patient allocation.

Evaluation

At the initial follow-up visit that was held a week after the hospitalization, patients with mTBI were asked for any complaints of memory loss. The details of the current study were explained to the eligible cases, and those who consented to participate after receiving informed consent were enrolled for further evaluation.

Data were gathered prior to the assessment includes demographics and site of trauma, previous surgical intervention, or medical disease. The first session were included of the patients' memory function evaluations by using the first episode of the AVLT questionnaire that was validated for Persian [11].

Then, patients were randomly assigned 1:1 into the treatment or the placebo groups using the random permuted blocks (block size of four). Following the random selection of a block, four patients were assigned according to the order of each block. Both Memoral and the placebo capsules were the same in size and weight. Both patients and the trial staff were

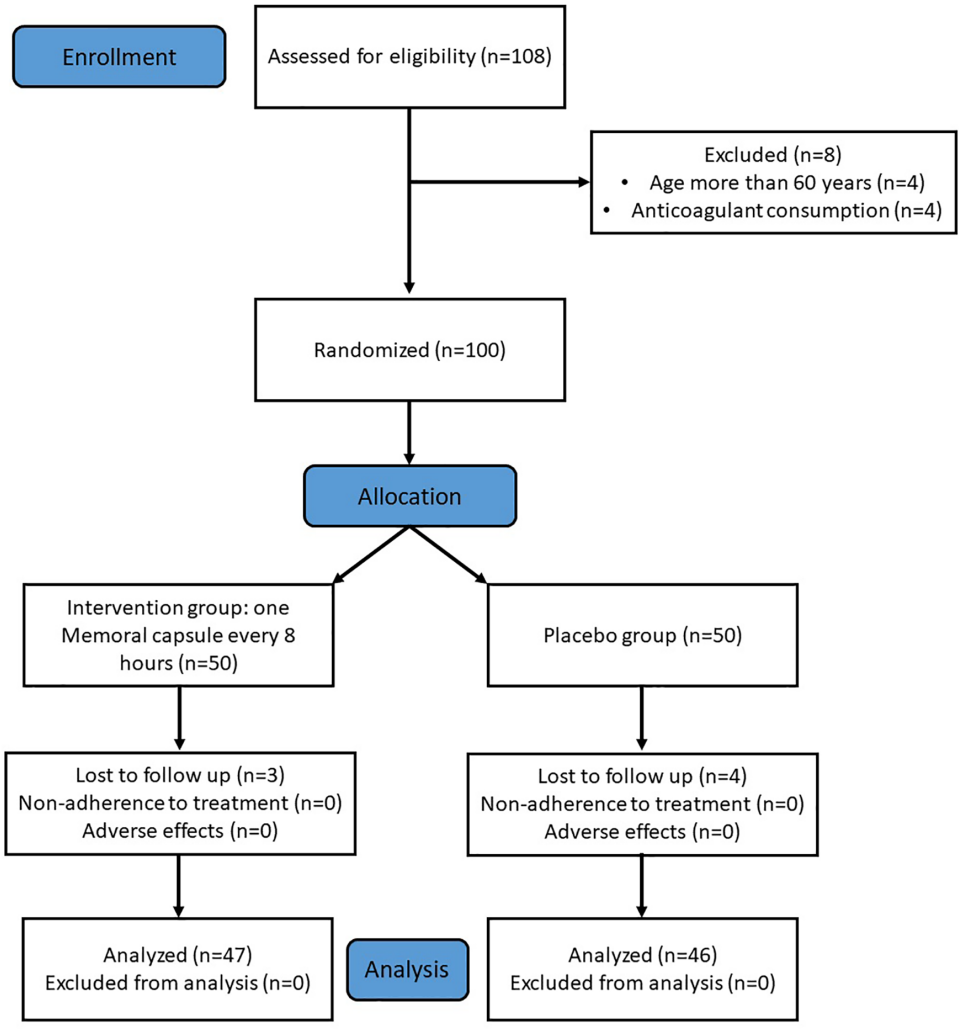

Fig. 1. Flow diagram of randomization and allocation of the patients

unable to distinguish them and were not informed about the contents of the capsules. Patients were asked to consume the medication every 8 hours for a month. After the complete consumption of 90 capsules (one month), patients were assessed using the second episode of the AVLT questionnaire. They were ensured about their conditions and were not prescribed any further medication.

The third step of the assessment was conducted two months after the second step, for which the third episode of the AVLT questionnaire was used.

Memory Assessment

The assessment of the memory function was conducted using the three episodes of the AVLT questionnaire, which was validated for the Persian language. A general practitioner, blinded to the contents of the given medication, was assigned to the assessment of the patients.

Each episode of this questionnaire is comprised of two different lists and 15 various words. The initial list would be read slowly five times, and after each session, patients were asked to mention any words that they recalled without any specific order. In the 6th step, the second list of words was read, and patients were asked again to tell the recalled words. Right after the assessment of the second list, patients were asked to tell any of the words from the first list (the words were not read at this step).

After a pause of twenty minutes without reading the words list, patients were asked again to mention any words that they recalled from the first list. Following these eight sessions, a list of 50 words was read to the patients, and they were asked to determine if the words were listed in the initial list or not.

AVLT Questionnaire Parameters

Word span (WS) is defined as the number of words that the patient recalls at the first step of the initial list assessment. The score of WS ranges between o to 15. Retroactive interference score (RIS) is defined as the difference between the number of recalled words in the sixth (which is assessed following the second list of words) and the fifth steps of the initial words list assessment. RIS is used to determine the inhibition degree of the new information from recalling the old ones and can be between -15 and 15.

Forgetting rate (FR) is defined as the difference between the number of recalled words between the seventh and fifth steps of the initial words list assessment. Its score varies between -15 to 15.

Total learning (TL) is defined as the total number

of words that a patient recall during the first five times of initial list assessments. The range of TL is between 0 to 75. Hit is defined as the number of words that were said to be in the initial list truly. The maximum score of Hit is 15.

Net positive score (NPS) is defined as the difference between the number of words that were said to be in the first list falsely and the number of words that were said to be in the first list truly.

Statistical Analysis

The statistical package of social science software (SPSS version 22, IBM Company, USA) was used to analyze the data, using the intention-to-treat method. Continuous variables were demonstrated as mean and standard deviation. Student T-test (two-tailed) was used to compare AVLT scores. The general linear model (GLM) repeated measures analysis was carried out to explore time, treatment, and time × treatment effects for AVLT scores between the two groups, assuming the study groups (treatment versus placebo) as the between-subject variable and the study outcomes at baseline and follow-up visits as the within-subject factor (time). Greenhouse-Geisser correction for degrees of freedom was reported if Mauchly's test of sphericity was significant. Partial eta squared (ηp2) was reported as the effect size. A p-value of <0.05 was considered statistically significant.

Results

A total of 1810 patients with the diagnosis of mild traumatic brain injury were referred to Rajaee hospital, a tertiary referral university-affiliated facility, over the course of seven months. Patients were screened in the first follow-up episode, held a week after hospital discharge. They were asked about any memory issue following the trauma, and among a total of 108 patients declaring complaints of memory disturbance, 100 eligible cases were included in the current study. Two groups of 50 patients were included in the treatment and control groups, with a mean age of 38.04±15.35 and 35.62±14.09, respectively (p=0.41). The demographics of the patients are illustrated in Table 1. The assessment of the memory function was performed as described at first, one-month, and three months follow-ups. During the follow-up sessions, seven patients were lost.

Comparing the scores of the three steps of the AVLT and regarding the change of scores from baseline to other follow-up intervals, it was revealed that patients who received Memoral for a month had better memory function, which was statistically significant.

The difference between the baseline and the one-month total learning score was 7.46±7.25 vs. 3.90±7.60 in the treatment and control groups, respectively (p=0.019). Such a significant difference was also observed in the difference between the third month and the baseline scores. (14.42±7.11 vs. 9.08±5.80. p<0.001). Evaluation of the RIS (which indicates the degree to which new information prevents the retrieval of old information) and FR (which evaluates long-term memory) showed a similar pattern to what was observed in TL.

In NPS, a score of the recognition step, patients in the treatment group had a significant improvement of the score in both the one and third-month assessments in comparison to the baseline (p=0.016 and p=0.002, respectively). WSP, which is a measure of attention and concentration, was improved in both follow-ups, but no statistically significant difference was observed at each interval.

The majority of treatment group patients subjectively mentioned an improved memory function at one-month follow-ups, whereas, most of the control group patients, claimed such an improvement at the third-month visits.

The details of scores at each interval and their comparison results are presented in Table 2.

Table 3 illustrates the effect of time, treatment and their mixture on the outcomes, using a general linear regression.

Figure 2 illustrates the change in scores for the parameters.

During the three months of follow-ups, not any medication-related adverse event was reported by the patients.

Discussion

TBI is regarded as the leading cause of mortality in many societies including Iran. Population-based researches show that TBI has an annual incidence rate of 15.3 to 144 per 100,000 people in Iran, with

Table 1. Demographics of patients.

Item		Treatment group	Control group	p value
Age		38.04±15.35	35.62±14.09	0.41
Years of education		12.08±2.7	12.7±2.95	0.277
Past medical history	Diabetes mellites	4	3	-
	Hypertension	7	4	
	Hypothyroidism	3	2	
Trauma point	Frontal area	30	32	-
	Occipital area	6	6	
	Temporal area	11	9	
	Parietal area	3	3	

Table 2. Comparison of AVLT scores between the two trial groups.

	Time points/periods	Treatment group (n=50)	Placebo group (n=50)	*p* value
Total learning	Baseline	32.66 (5.32)	32.24 (4.80)	0.680
	Month 1	40.12 (6.17)	36.14 (5.83)	0.001
	Month 3	47.08 (4.63)	41.32 (3.67)	<0.001
	Change from baseline to month 1	7.46 (7.25)	3.90 (7.60)	0.019
	Change from baseline to month 3	14.42 (7.11)	9.08 (5.80)	<0.001
Word span	Baseline	6.30 (1.69)	6.26 (1.27)	0.894
	Month 1	6.52 (1.31)	6.60 (1.14)	0.746
	Month 3	8.88 (2.26)	8.22 (2.21)	0.144
	Change from baseline to month 1	0.22 (1.64)	0.34 (1.28)	0.685
	Change from baseline to month 3	2.58 (2.90)	1.96 (2.38)	0.246
Retroactive interference score	Baseline	3.12 (2.02)	3.02 (2.08)	0.808
	Month 1	1.58 (1.12)	2.70 (1.92)	0.001
	Month 3	1.12 (0.96)	2.30 (1.47)	<0.001
	Change from baseline to month 1	1.54 (2.17)	0.32 (2.78)	0.016
	Change from baseline to month 3	2.00 (2.08)	0.72 (2.37)	0.005
Forgetting rate	Baseline	4.08 (2.05)	3.80 (2.39)	0.533
	Month 1	3.30 (2.06)	4.20 (2.01)	0.029
	Month 3	2.04 (1.36)	3.28 (1.29)	<0.001
	Change from baseline to month 1	0.78 (2.77)	-0.40 (3.00)	0.044
	Change from baseline to month 3	2.04 (2.38)	0.52 (2.62)	0.003
Net positive score	Baseline	2.20 (2.43)	2.40 (2.84)	0.707
	Month 1	4.46 (1.90)	3.16 (2.33)	0.003
	Month 3	6.34 (2.36)	4.26 (2.89)	<0.001
	Change from baseline to month 1	2.26 (2.56)	0.76 (3.47)	0.016
	Change from baseline to month 3	4.14 (2.98)	1.86 (4.22)	0.002
HIT	Baseline	5.96 (2.02)	5.92 (1.95)	0.960
	Month 1	6.82 (1.85)	6.14 (2.06)	0.086
	Month 3	7.60 (1.73)	8.00 (1.90)	0.276
	Change from baseline to month 1	0.86 (2.76)	0.20 (3.20)	0.273
	Change from baseline to month 3	1.64 (2.67)	2.06 (2.86)	0.450

[a]P-value of <0.05 was considered statistically significant; Data are shown as mean (standard deviation).

Table 3. Results of GLM repeated measures analysis on AVLT scores.

	Factors					
	Time		Treatment		Time×Treatment	
	F	η_p^2	F	η_p^2	F	η_p^2
Total learning	135.0[a]	0.58	30.5[a]	0.23	7.23[b]	0.06
Word span	205.1[a]	0.38	0.85	0.009	1.57	0.16
Retroactive interference score	21.8[a]	0.18	10.4[b]	0.09	5.8[b]	0.05
Forgetting rate	13.9[a]	0.12	7.05[b]	0.01	4.6[c]	0.04
Net positive score	42.2[a]	0.30	10.7[b]	0.09	6.2[b]	0.06
HIT	22.17[a]	0.18	0.25	0.003	1.81	0.01

[a]*p* value<0.001; [b]*p* value<0.01; [c]*p* value<0.05

the affected age range being 21 to 40 [3, 12]. The most common type of TBI, widely recognized as mild traumatic brain injury (mTBI), accounts for around 75-85 % of all TBI cases [13].

In addition to the social and financial costs of mTBI, it can cause issues in a variety of dimensions of the patient's life. Post-concussion syndrome, including problems with cognition, physical issues, emotional control, etc., can take place and last in up to 85% of cases, regarding the different reports [2, 4]. The etiology of PCS is not clearly defined. However, diffuse axonal damage in higher cortical regions and the hippocampus have been mentioned to be the underlying causes [5, 14, 15]. It is believed that most of the PCS would be alleviated in up to three months, but they can turn persistent in about ten percent of occasions [16].

mTBI can cause changes in different aspects of brain function. The study of Sun *et al*., [17] showed that an increase in inflammation-related cytokines (such as IL-6 and IL-1B) following the mTBI can be expected. More severe post-concussion syndromes were also observed among patients with higher levels of these cytokines [18]. Other functional studies also

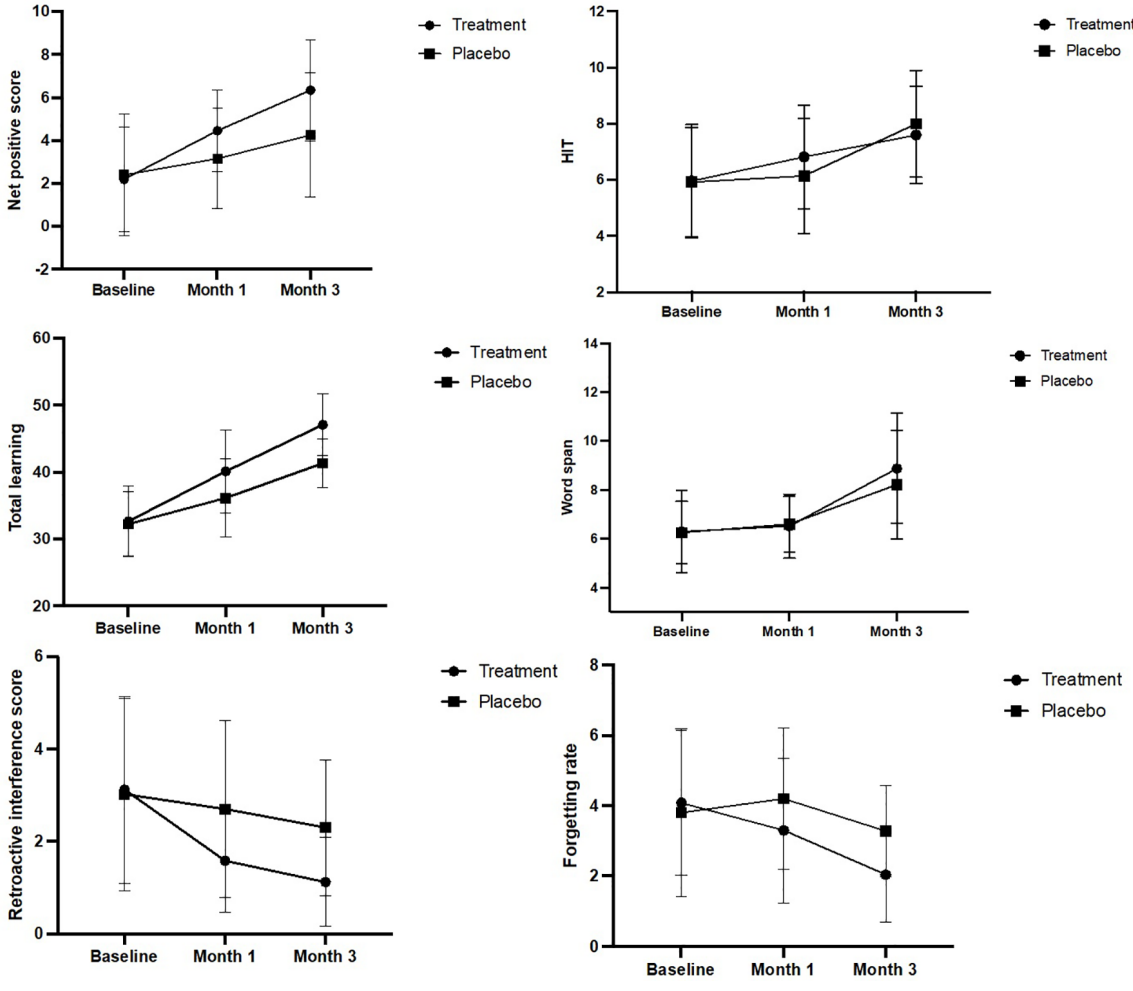

Fig. 2. Changes in the AVLT parameters

revealed changes in cerebral cortex circulation and glucose metabolism [19, 20].

It seems that trauma-induced inflammation has a determining effect on the severity of the post-concussion symptoms. A study by Ganti *et al*., [21] showed that patients who had alcohol consumption after TBI had a slower neurological recovery, which was attributed to the increased inflammatory state. It might come to mind that the direct location of the injury has a most important role in causing the PCS and related symptoms, such as memory disturbance. But, some studies have proven that patients with direct trauma to the frontal lobe had no significantly different memory function in comparison to others [22].

Previously some interventions like noninvasive and also invasive brain stimulation and the application of antioxidative agents such as vitamin E have been used to alleviate memory impairment following mTBI [23, 24]. Memory dysfunction following mTBI is an irritating symptom that can also become chronic [4]. In the current study, we evaluate the effect of a mixture of 360 mg of Boswellia gum resin and 36 mg of ginger root granule powder in the current study as there have been no reports on the medical therapy for this issue.

Boswellia has been shown to have anti-inflammatory and anti-oxidative effects [25]. It can reduce PGE2 formation, which leads to a reduction in inflammation [26]. There are many reports of the Boswellia application in different medical disorders, such as asthma, arthritis, and inflammatory bowel disease [26, 27]. Since the old times, there has been a belief that Boswellia can improve memory function and intelligence. Different studies have surveyed the effect of Boswellia on the hippocamp and memory function [28, 29]. The positive effects of Boswellia have been proved on different memory aspects in rats [30]. There are also numerous reports of Boswellia enhancing the memory function, in a setting of different underlying pathologies [31, 32].

The anti-degenerative effect of Boswellia on the hippocampus and its role in forming new neural networks has been assumed as the underlying mechanism through, which it can cause improvement in memory function [28, 33]. High dosages of Boswellia may cause platelet aggregation, headache, and bowel irritation, which was not observed in our series [34].

Ginger, the other component of Memoral has been also shown to have anti-inflammatory and anti-oxidative effects [35]. Ginger and its active components can affect neurotransmitters. They increase dopamine, acetylcholine, and serotonin levels in the cortex and the hippocampus [36]. An

induced increase in levels of acetylcholine and monoamines has been shown to improve cognitive processes [37]. The positive effect of Ginger have been subjected to different reports on age-related neurological disorders and patients with memory disturbance following various disorders like ischemic strokes [36, 38].

High levels of ginger can cause gastrointestinal upset, restlessness, and sleepiness, and it can interact with anticoagulants and analgesics [39]. It is worth mentioning that none of the documented side effects of Boswellia and ginger was observed in our series.

Compared to previous studies which have evaluated the memory function of the patients after mTBI, patients in our series had a lower initial score. This issue might be attributed to the selection of the patients, where only those with subjective memory complaints were included [24, 40]. Repeated quantitative assessment using the AVLT questionnaire showed a gradual recovery and improvement of memory function among our patients, which is congruent with previous studies.

Comparing the two groups in our study, patients receiving the herbal medication mentioned the subjective feeling of improvement in short and long-term memory function, which was also proved in the assessment using the questionnaire. While on the other hand, the changes in the scores of the placebo group, at the end of three months, despite its increasing pattern, were significantly lower in comparison to the treatment group.

Our study revealed a statistically significant difference between the treatment and control groups in the change of memory scores as measured quantitatively by the AVLT questionnaire. For mTBI patients with memory problems, a Boswellia and Zingiber combination appears to be helpful in hastening the recovery of their memory while posing almost no complications.

Limitations

For the current study, according to the previously mentioned statistical methods, the minimum number of cases that were sufficient for participation was included. Similar studies by recruiting a larger population and also using multi-center databases would have provided a more precise comparison of the control and intervention groups.

Declarations

Ethics approval and consent to participate: The trial received approval from the Shiraz University of Medical Sciences Ethics Committee with the ethics code of IR.SUMS.REC.1400.756 and has been also registered in the Iranian Registry of Clinical Trials with the registry number IRCT20130310012776N8. The informed consent for participation and publication was obtained from all patients.

Consent for publication: The informed consent for publication was obtained from all patients.

Conflict of interests: All authors state that they have no competing interests in this work.

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Authors' contributions: All Authors contributed in different stages of the manuscript preparation, and they all approved the submission.

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