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Effects of Boswellia serrata on Improvement of Memory Impairment in Patients with Mild Cognitive Impairment: A Double-blind, Randomized, Placebo-controlled Study

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Abstract

Background: Mild cognitive impairment (MCI) is the stage between the expected cognitive decline of normal aging and the more serious decline of dementia. In the present study, the effect of Boswellia serrata (BS) on improvement of memory impairment in patients with MCI was investigated.

Methods: In this single-center randomized double-blind placebo-controlled clinical trial study, 118 patients with mild cognitive impairment (MCI) were included and randomly divided into two groups (case and control). Control group (n=59) received BS 300 mg/kg body weight twice a day and control group (n=59) received placebo for a period of three and six months. Montreal Cognitive Assessment (MoCA) test for detecting cognitive impairment was done at baseline, three and six months after the intervention.

Results: A significant difference was reported in the MoCA mean score between the groups after three months (24.64 vs. 22.83) and six months of the intervention (25.22 vs. 22.7). Memory item had the greatest impact on the average final score (P≤0.0001).

Conclusion: BS has a significant effect on the improvement of memory impairment in patients with MCI. Further studies are required with higher doses of BS and longer duration of treatment to assess the effects of BS on memory of patients with MCI.

Introduction

Mild cognitive impairment (MCI) is an intermediate stage between the expected cognitive decline of normal aging and the more serious decline of dementia. Generally, these changes are not severe enough to interfere with normal daily life activities (1,2). MCI may increase the risk of progression to dementia, caused by Alzheimer's disease or other neurological disorders. Some forms of MCI are observed in 40% of the patients with cognitive impairment (3). MCI affects patients' quality of life. It is probably the most important determinant of employment status and associated societal costs, and also, it adversely affects driving safety, household task completion, social activity, physical independence, rehabilitation progress, coping, treatment adherence, and mental health (3). Various factors like inflammatory process and high blood pressure are known to produce MCI (1). The main value of identifying such patients in an asymptomatic period of Alzheimer's disease is taking early treatment measures (4). Mild cognitive

abnormalities are not usually apparent through a routine office visit and need more sophisticated neuropsychiatric assessment (3). According to the anti-inflammatory properties of Boswellia serrata (BS) extract supported by some clinical trials, traditional medicine is getting more attention to use BS in MCI management (5,6). Recent studies have shown that BS has a protective effect on neurons (6-8). It can enhance the structural formation of new neural networks. Since neurodegenerative diseases like Alzheimer's disease lead to the destruction of these networks, and consequently, loss of cognitive ability, this traditional herb can be considered effective in the treatment of the disease (9-11).

BS is an Iranian traditional medicinal herb. Some initial studies in Iran have reported positive effects of this herbal medicine on the enhancement of cognition in rats (8). Since BS has antioxidative effects, it has been suggested for improving cognitive impairment (6). To the best of authors' knowledge, there is no clinical study on the BS effect on cognitive impairment in patients with MCI using Montreal Cognitive Assessment (MoCA) test (12). Therefore, the present study was conducted to investigate the effectiveness of BS in preventing dementia in patients with MCI using MoCA test.

Various tests including Montreal Cognitive Assessment (MoCA) and Mini-Mental Status Examination (MMSE) tests have been designed to assess cognitive impairment in patients (12,13). MoCA test is superior to the MMSE for detection of MCI. The sensitivity of MMSE and MoCA tests in detecting MCI was 18% and 90%, respectively (12). In the group with mild Alzheimer's disease, the sensitivity of MMSE and MoCA tests was 78% and 100%, respectively (13). Therefore, MoCA test was selected for this study. MoCA test was developed as a brief screening tool to detect MCI (12). It is a paper-and-pencil tool that requires approximately 10 minutes to administer and is scored out of 30 points. MoCA test assesses multiple cognitive domains including attention, concentration executive functions, memory, language, visuospatial skills, abstraction, calculation, and orientation. It is widely used around the world and has been translated into 36 languages and dialects. The test and its instructions are freely available on the MoCA official website (www.mocatest.org) and no permission is required for its clinical or educational use. The average MoCA score for MCI is 22 (range: 19-25). MoCA test has been validated for people aged 55-85 years (12).

At present, no medicine or treatments are specifically approved by the Food and Drug Administration (FDA) for MCI. Clinical studies are being conducted to find demonstrable treatments that may improve symptoms or prevent or delay progression to dementia (4,14). Therefore, this study was conducted to examine the effectiveness of BS in preventing dementia in patients with MCI using MoCA test. Specifically, it was hypothesized that patients taking BS would have better MoCA scores than those who did not take it and reporting significant complications (Hypothesis 1). Furthermore, it was hypothesized that patients receiving BS would report better scores in the majority of the components of MoCA test (Hypothesis 2). Next, it was hypothesized that patients taking BS would report the greatest score in memory component of MoCA test (Hypothesis 3). Finally, it was hypothesized that the effects of BS would be most pronounced with higher doses of BS and more prolonged duration of treatment (Hypothesis 4).

Materials and Methods

Patients with MCI who were diagnosed at the Neurology Clinic of Shafa Hospital in Kerman, Iran, were invited to

participate in the present study. In this study, 120 patients were diagnosed with MCI by a neurologist in dementia field according to Petersen criteria and MoCA test. Patients who did not take any drugs with central nervous system (CNS) effects were included in the study. Treatable diseases such as brain tumor, hematoma, hypothyroid, liver and renal diseases, neuroinflammatory disorders that could simulate MCI were excluded by brain MRI and laboratory tests (TSH, AST, ALT, BUN, Cr, Ca, CBC, ESR, CRP, and FBS). Depression was also assessed using Beck Depression Inventory (BDI) (15).

The inclusion criteria for patient selection include:

1. Confirming MCI by Petersen criteria (2),
2. Lack of contraindication like gastric ulcer for taking Boswellia serrata (16),
3. Beck test score >7; i.e. the patient does not have depression (15),
4. Lack of any lesions in brain MRI, justifying cognitive impairment (17),
5. Normal lab data including CBC, ESR, CRP, TSH, AST, ALT, BUN, Cr, Ca, and FBS (1),
6. Patients with age of 55-85 years who did not take any drugs with CNS effects.

After obtaining a written informed consent form, MoCA test was performed on the selected patients. Then, the patients were randomly divided into two different groups of case and control.

In a study by Hosseini-Sharifabad et al. (2011), BS was given to male rats with cognitive impairment due to hyperthyroidism with a dose of 500 mg/kg for six months (10). Also, in another study by Sedighi et al. (2014), the patients received BS (300 mg/kg body weight) twice a day (22). In different clinical studies, the efficacy of BS extract with a dose of 300 mg/kg three times a day was comparable with that of Sulfasalazine and Mesalasine for treating crohn's disease and ulcerative colitis (23-25). In order to prevent side effects of BS such as nausea, reflux, and gastrointestinal disorders (6), it was decided to use this extract with a dose of 300 mg/kg body weight twice a day for three months in this study.

The case group received a capsule containing 300 mg/kg body weight BS twice a day(8) and the control group received a capsule with the same size, color, and shape but containing starch without BS active gradient. Both capsules were made in the Pharmacology Research Center, Kerman University of Medical Sciences, Kerman.

The patients were asked to continue their routine treatments of hypertension and/or diabetes mellitus matched between the two groups and to inform the research team in the case of receiving another treatment during the follow-up period. In the case of any side effects or problems, the patient was withdrawn from the study. After three and six months of treatment, MoCA test was repeated and the obtained data were analyzed using independent sample t-test. Statistical comparisons were performed using SPSS version 22. For all analyses, statistically significant value was considered at $P<0.05$.

Results

In the present study, 120 patients with MCI (90 male, 30 female) aged 55-67 years (Mean age= 68.51 years with Standard Deviation= 5.14) were randomly divided into two groups (case and control) after performing MoCA test. Two patients from both groups, dropped out of the study due to dyspepsia. Therefore, 59 patients in each group were able to finish the study. After three and six months of intervention and repeating MoCA test, the following results were obtained.

The mean age of the patients was 68.51 ± 5.14 years and 75.4% (n=118) of them were male. There was no significant difference between the two groups in terms of age (P=0.71), sex (P=0.34), and level of education (P=0.32). The mean age of patients in case group was 66.59 ± 8.4 years and 67.8% (n=40) of them were male. In control group, the mean age of the patients was 68.42 ±8.5 years and 76.3% (n=45) of them were male. As shown in Figure 1, in the case group that received BS, the change in MoCA mean score before, 3 and 6 months after the intervention was statistically significant (P<0.001). But, in the control group, this change was not statistically significant (P=0.12). The mean score of MoCA test before, 3 months and 6 months after the intervention in the case and control groups were respectively 22.89, 24.64, 25.22 vs 22.74, 22.83, 22.7. MoCA test included Trial, Cube, Memory, Fluency, Clock, Naming, Serial, and Abstract components. The results showed that the mean difference in" alternating trial making" and" Memory" components before and 6 months after the intervention were respectively -0.49 and -2.10, which were statistically significant (P<0.001, Figure 2). In this study, most patients (n=56) had high school diploma and the minority of them (n=11) had master's or doctoral degree (Table 1).

Table 1. Distribution of education level in patients with mild cognitive impairment

Variable	Group	Case		Control	
		Frequency	%	Frequency	%
Education	Illiterate	12	20.3	16	27.1
	Diploma	34	57.6	22	37.3
	Associate degree	9	15.3	14	23.7
	Bachelor's, Master's degree and higher	4	6.8	7	11.9

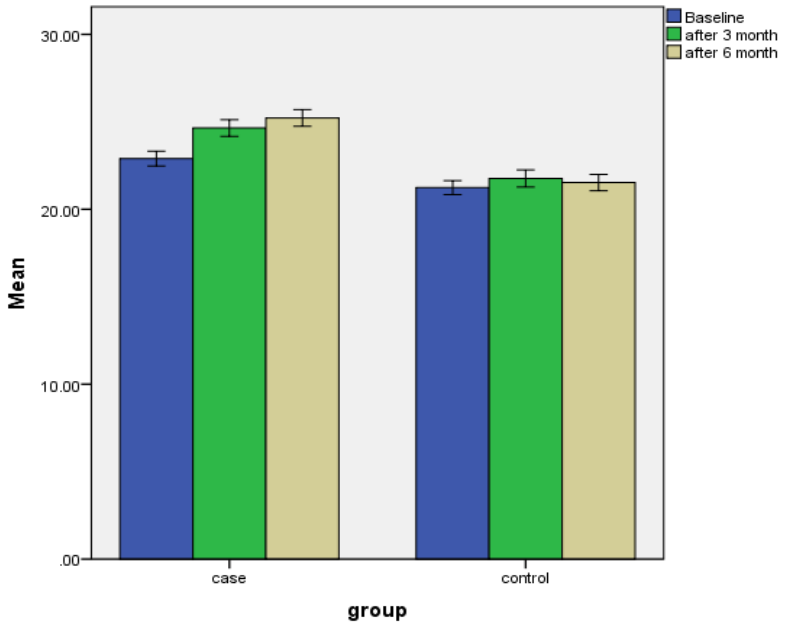

Figure 1. Mean score of MoCA test at baseline and after three and six months in case and control groups.

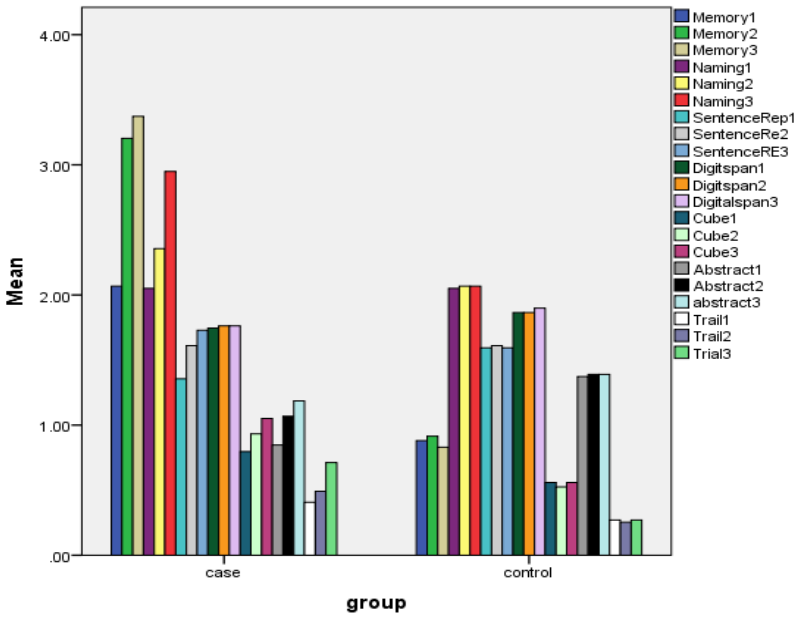

Figure 2. Mean score of MoCA components shown at baseline, three and six months after intervention in case (receiving Boswellia serrata) and control (receiving placebo) groups. MoCA components before receiving Boswellia serrata include Trial1, Cube1, Abstract1, Naming1, Memory1, Sentence Repeat1, and Digitspan1. MoCA components three months and six months after receiving Boswellia serrata include Trial2, Cube2, Abstract2, Naming2, Memory2, Sentence Repeat2, Digitspan2, and Trial3, Cube3, Abstract3, Naming3, Memory3, Sentence Repeat3, and Digitspan3, respectively.)

Discussion

MCI has inflammatory and neurodegenerative causes which lead to the formation of tau plaques in the brain tissue (18,19). Oxidative stress accompanied by depletion of endogenous antioxidants is known as the cause of cognitive impairment (18,19). BS is a resinous extract from the trees of the genus Boswellia. BS consists of 25-35% alcohol-insoluble resin, 60-70% resin, and essence. Bosolic acids are groups of pentacyclic triterpenoids. These acids are the most important part of resin in BS. Bosolic acids consist of 11-keto-β-boswellic acid, beta bosolic acid, and 3-acetyl-11-keto-β-Boswellic acid (10). Anti-inflammatory effects of BS are due to triterpenoid acids, especially beta-bosolic acids (20). The anti-inflammatory effects of BS lead to the improvement of cognitive impairment in Alzheimer's disease (21). The efficacy of cholinesterase inhibitors like Donepezil, Rivastigmine, Galantamine, and Vitamin E in MCI patients has not been approved (14). The effects of these expensive and synthetic drugs with many side effects are limited in the improvement of memory. Therefore, the use of traditional medicine such as BS is a logical solution. In this study, patients who received BS in comparison with control group showed a significant improvement in short-term memory as measured by MoCA test (memory item). Also, there was a significant improvement in visual-constructional skills as measured by MoCA test (Cube & Clock items) (17).

The results of the present study relatively confirm the results of a study conducted on healthy volunteers indicating that BS improves verbal and logical memory (Taghizadeh et al. 2017). Other studies by Farshchi et al. (2010) and Mahmoudi et al. (2011) showed that BS has a significant effect on the improvement of spatial learning in rats (8,10). Also, a study by Sedighi et al. (2014), showed that BS is probably effective in improving visual-spatial memory (BVMT-R) in MS patients (22). Although various researchers have established the anti-inflammatory, anti-arthritis, and other effects of BS, the findings of the present study shed more light on the justification

of the traditional use of BS in managing dementia and other neurodegenerative disorders. The reason that, BS in the present study could not improve all MoCA test items might be attributed to the dose-dependent effect of BS, which was identified by Farshchi et al. and Mahmoudi et al. (8,10). They observed that the effect of BS on visual memory in rats was dose-dependent. Therefore, further studies are suggested to evaluate the effects of various doses and methods of administration (powder or syrup) on cognitive items. The administration of BS for a longer duration with higher doses and in syrup form might be more effective in improving cognitive decline (6). Therefore, by increasing treatment duration and dose, the effects of this drug on other cognitive skills might be more prominent.

Therefore, further studies are recommended to evaluate the effects of BS on the improvement of cognitive impairment and prevention of dementia in patients with MCI.

Conclusion

According to the results, the memory item of MoCA test was significantly improved after administration of BS in patients with MCI, but further clinical studies with higher doses of BS in other forms (encapsulated or syrup) and longer administration duration are recommended to evaluate the potential treatment effects of BS in patients with MCI.

It was also concluded that higher education levels and cognitive reserve may be protective factors for MCI and Alzheimer's disease (26).

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Article Notes

Some of the results described in this article were presented at the 19th Annual Congress of Iranian Neurology Association, Tehran, Olympic Hotel, May 2014. Requests for additional information and access to the research materials may be addressed to the corresponding author.

Conflicts of Interests

The authors declare that they have no conflicts of interests.

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Ethical Approval

The present study was approved by the Ethics Committee of Kerman University of Medical Sciences (Ethical code: K/92/315, Iranian clinical trial (IRCT) code: IRCT201402088430N8).

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