

Comparing efficacy and safety of *Crocus sativus L.* with memantine in patients with moderate to severe Alzheimer's disease: A double-blind randomized clinical trial

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Alzheimer's disease (AD), the leading cause of dementia worldwide, is an irreversible progressive neurodegenerative disorder characterized by cognitive impairment, and functional disability. Management of the severe stages of Alzheimer's disease is a great challenge and limited pharmacological options are currently available. The dried stigma of *Crocus sativus L.*, called saffron, can target some pathologic processes of AD and its cognitive-enhancing properties have been evidenced in different studies. We previously investigated the efficacy and safety of saffron for mild to moderate AD in two separate clinical trials (1, 2). Interestingly, saffron constituents have been shown to decrease extracellular glutamate levels and exert antagonist effects on NMDA receptors; a function which can be compared to memantine's mechanism of action. We aimed to compare the efficacy and safety of saffron versus memantine in reducing cognitive deterioration of patients with moderate to severe AD.

In this randomized double-blind parallel-group study (non inferiority design), 68 patients with moderate to severe AD (Mini Mental State Examination score: 8-14) were randomized to receive memantine (20 mg/day) or saffron (30 mg/day) for twelve months. Participants were evaluated monthly by the Severe Cognitive Impairment Rating Scale (SCIRS) and Functional Assessment Staging (FAST) in addition to recording probable adverse events. The trial protocol was approved by the institutional review board of Tehran University of Medical Sciences and performed in accordance with the Declaration of Helsinki and its subsequent revisions. General linear model repeated measures analysis was used in order to assess effect of time \times treatment interaction, considering the treatment group (saffron vs. memantine) as the between-subject factor and the study measurements as the within-subject variables (time).

One hundred and fourteen individuals were screened for the eligibility criteria and sixty-eight patients were randomized into two groups. One patient in each group died during this trial due to reasons not related to the study and a total number of sixty patients (saffron=30, memantine=30) completed the trial. Both treatment groups showed similar behaviour during this trial as demonstrated by insignificant effects for time \times treatment interaction on SCIRS scores as our primary outcome measure [$F(2.95, 194.78)=2.25, P=0.08$]. There was no significant difference between the two groups in score changes from baseline to the endpoint on SCIRS ($P=0.38$) and FAST ($P=0.87$). Patient vital signs, laboratory tests, and ECG did not change significantly from baseline to the final visit. Based on the adverse events checklist, a total number of seven side effects were reported during this trial which were all mild and resolved spontaneously without any intervention. No significant difference was detected between two groups in the frequency of the adverse events.

In addition to its favourable safety profile, one year administration of saffron capsules showed to be as effective as memantine in reducing cognitive decline in patients with moderate to severe AD. Confirmatory studies with larger sample sizes and longer follow-up periods are warranted.

(1) Akhondzadeh S et al., *J Clin Pharm Tehr* 25: 581, 2010.

(2) Akhondzadeh S et al, *Psychopharmacology* 207: 637, 2010