JALALABAD MEDICAL JOURNAL

Original Articles

Efficacy and Tolerability of Donepezil in the Patients with Mild-to-Moderate Dementia: an Interventional Study

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ABSTRACT

Dementia is the loss of memory and other cognitive abilities severe enough to interfere with day-to-day functioning. It is brought on by an alteration in the nervous system. Although there are several varieties of dementia, Alzheimer's disease is the most prevalent. Pharmacological agent cholinesterase inhibitors (ChEIs) have been used globally and have demonstrated efficacy in treating dementia patients. The objective of the study was to evaluate the efficacy and tolerability of donepezil for patients with mild to moderate dementia. This interventional study was conducted from July 2017 and June 2018 in neurology, psychiatry, and medicine outdoor of Sylhet MAG Osmani Medical College Hospital, Sylhet. A total of 102 dementia patients were enrolled by purposive sampling. Patients diagnosed with mild-to-moderate dementia, regardless of gender, were prescribed donepezil 5 mg once daily for 20 weeks. Initially, 110 patients were included; however, finally, data from 102 patients were analysed. Cognitive functions of the patients were measured using the Mini-Mental State Examination (MMSE) score at the completion of the fourth, twelfth, and twentieth weeks. Evaluations of safety and tolerance of donepezil include keeping monitor of and documenting any adverse effects following the treatment. The mean MMSE score at the start of the donepezil treatment was 15.05±3.49. At four, twelve, and twenty weeks of treatment, the scores were raised significantly ($p<0.001$). The percentage change in the MMSE score developed significantly ($p<0.001$) over the course of the 20-week treatment. As therapy progressed, adverse effects decreased significantly ($p<0.05$). Donepezil at the prescribed dosage is effective and well-tolerated for mild to moderate dementia.

Keywords: *Donepezil, Dementia, MMSE score, Alzheimer's disease, Acetylcholinesterase inhibitors.*

[Jalalabad Med J 2024; 21 (2); 57-61]; DOI: https://doi.org/10.3329/jmj.v21i2.83217

INTRODUCTION

Loss of previously acquired intellectual capacity without a decrease in alertness is the hallmark of dementia[1]. Dementia results in a progressive, long-term loss of thinking and memory capacity. Alzheimer's disease accounts for 50% to 70% of instances of dementia, making it the most prevalent cause. Other prevalent forms are frontotemporal dementia, Lewy body dementia, and vascular dementia[2]. Patients with dementia undergo a variety of tests, such as blood

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testing for thyroid, liver, and kidney function as well as HbA_1c, vitamin B_{12}, and folate levels. In addition to these tests, imaging techniques like CT or MRI scans of brain can be performed[3]. Simple and quick tests, such as the Mini-Mental State Examination (MMSE), which is a brief bedside cognitive assessment, are more suitable for determining the degree of dementia at the primary and secondary levels of care[4].

Patients with dementia have been found to have decreased levels of choline-acetyltransferase (ChAT)[5]. A significant factor in the cognitive impairment seen in elderly people with Alzheimer's disease (AD) is a malfunction of cholinergic neurons in the brain[6]. In individuals with dementia, acetylcholinesterase inhibitors (AChEIs) have been employed as the first line of treatment. Galantamine, rivastigmine, and donepezil are the three common ChEIs. By reducing the activity of acetylcholinesterase inhibitors, these ChEIs improve cholinergic transmission by increasing the amount of acetylcholine available for interaction with postsynaptic acetylcholine receptors[7]. A selective and reversible acetylcholinesterase inhibitor is donepezil. These acetylcholinesterase inhibitors raise acetylcholine levels in the synapses to enhance cognitive performance[8]. Although, donepezil is associated with some adverse effects, such as appetite loss, vertigo, fatigue, weakness, sleep disturbances, tremors, and muscle cramps[9].

There are few data on donepezil's effectiveness as a treatment in dementia patients in our country. Therefore, this study aimed to evaluate the efficacy and tolerability of donepezil for patients with mild to moderate dementia.

MATERIALS AND METHODS

This interventional study was conducted at Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh, from July 2017 to June 2018 in the departments of pharmacology and therapeutics in collaboration with the departments of neurology, psychiatry, and medicine. The study population consisted of all patients with mild-to-moderate dementia, both genders, who visited the outpatient departments of medicine, neurology, and psychiatry. Patients with bronchial asthma, benign enlargement of the prostate, myocardial infarction, peptic ulcer disease, and a current diagnosis of any further severe neurologic and psychiatric disorder other than dementia were excluded. Purposive sampling method was implied for the collection of data. Ethical permission was taken from the ethical committee of Sylhet MAG Osmani Medical College. Following a thorough explanation of the study procedure and the aim of the study, informed written consent was obtained from the patient's legal guardians. A total of 110 participants initially took part in the study. A self-made data sheet was used to collect the data. Donepezil 5 mg once daily for 20 weeks was given to the patients. Cognitive function was assessed by using the Mini-Mental State Examination (MMSE) scale, with baseline scores obtained at the 4^{th}, 12^{th}, and 20^{th} weeks. The evaluation of safety and tolerability encompasses the systematic observation and record-keeping of every adverse event, encompassing any unwanted symptoms, indicators, or medical disorders. Every patient was monitored through either telephone communication or in-person visits to their residence, with a prearranged appointment, in order to ensure effective follow-up. During the duration of the study, a total of 8 patients were excluded from the study due to non-compliance with the study protocol. Ultimately, a total of 102 patients' data were subjected to analysis. Statistical analysis was carried out using SPSS (Statistical Package for Social Science) version 22. Quantitative data was expressed using the mean and standard deviation. A comparison between the pre and post MMSE score measurement was conducted using repeated measures ANOVA (Analysis of Variance), and comparison from baseline to 4^{th}, 12^{th} and 20^{th} weeks was conducted by Bonferroni's post hoc test. The qualitative data was expressed using frequency and percentages and analysed by Fisher's Exact test.

RESULTS

About 54% of the study population had Alzheimer disease and 46% had vascular dementia (Figure-1). At the beginning of donepezil treatment, the mean MMSE score was 15.05±3.49. Gradually, the score increased about 15.84±3.86, 19.19±4.38 and 20.05±1.11 at 4^{th}, 12^{th} and 20^{th} weeks, respectively. The mean MMSE score was significantly increased at 12^{th} weeks and 20^{th} weeks of treatment ($p<0.001$) (Table-I). Bonferroni's post hoc test revealed that the mean MMSE score exhibited a substantial increase after 12 weeks.

The percentage change in MMSE score was measured at 4^{th}, 12^{th} and 20^{th} weeks of donepezil treatment and the result showed that throughout the 20^{th} week of treatment, the percentage change in MMSE score was increased significantly ($p<0.001$) (Figure-2).

Regarding side effects of donepezil, at the 4^{th} week of treatment, 7.8% of patients complained of nausea, which gradually decreased in the 12^{th} week (2.9%)

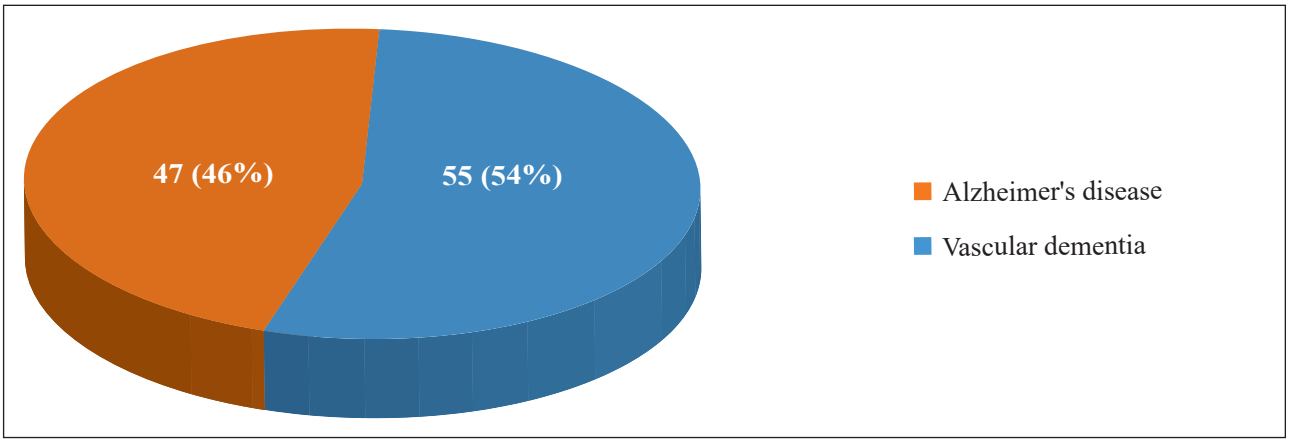

Figure-1: *Distribution of patients according to clinical diagnosis, n=102.*

and 20th week (0.98). At 4th weeks, 4.9% complain of vomiting, which also decreased in 12th weeks (2%) and 20th weeks (0%). At the same time, 5.9% of patients complained of diarrhoea, which decreased gradually in 12th weeks (2%) and 20th weeks (0%). As the treatment progressed, the side effects decreased significantly ($p<0.05$) (Table-II). There was no hypersensitivity reaction in any patient.

Table-I: *Effects of donepezil on MMSE score, n=102.*

Duration of donepezil use	MMSE score (Mean±SD)	*p-value
At Baseline	15.05±3.49	
At 4th week	15.84±3.86	<0.001
At 12th week	19.19±4.38	
At 20th week	20.05±1.11	

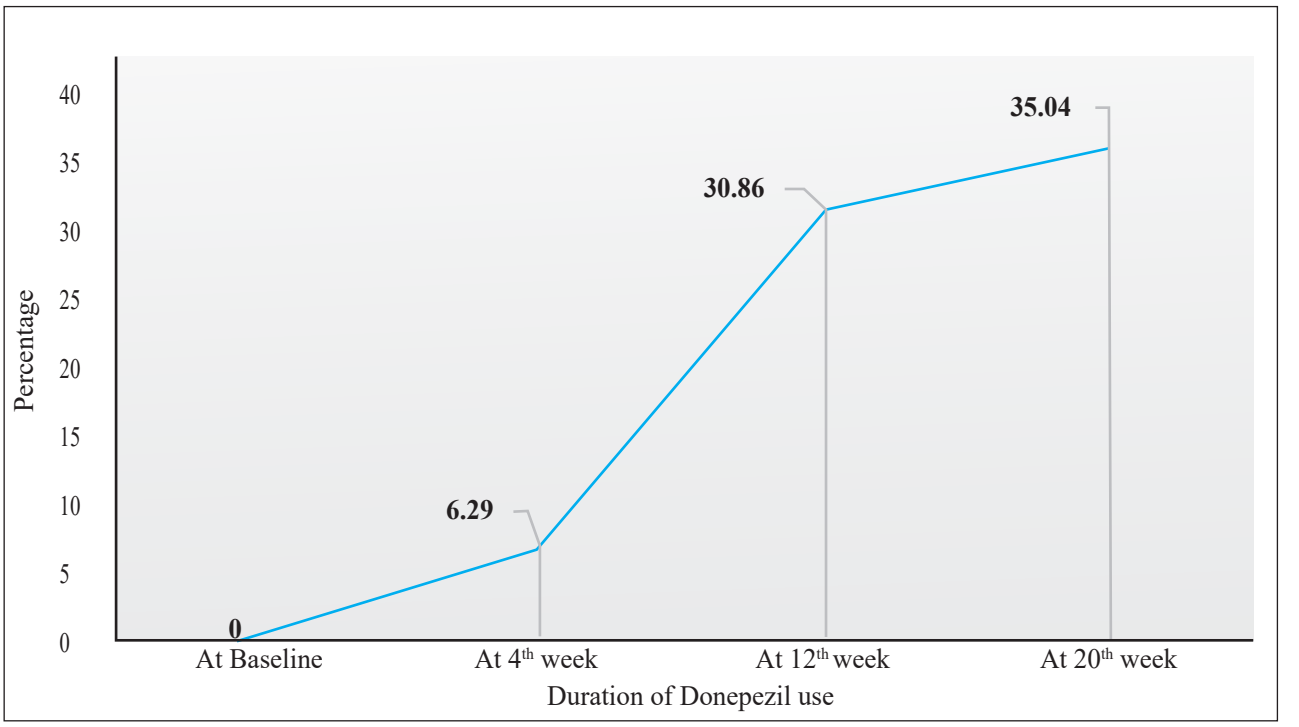

Figure-2: *Percentage change in MMSE score measured at 4th, 12th and 20th week of treatment compare to before initiation of treatment, n=102.*

*Repeated measure ANOVA was applied to analyse data.

Table-II: *Adverse effect of donepezil at different weeks, n=102.*

Adverse effects	4th week, n (%)	12th week, n (%)	20th week, n (%)	*p-value
Nausea	8 (7.8)	3 (2.9)	1 (1)	<0.05
Vomiting	5 (4.9)	2 (2)	0 (0)	
Diarrhoea	6 (5.9)	2 (2)	0 (0)	
Dizziness	7 (6.9)	4 (3.9)	2 (2)	

*Fisher's Exact test was applied to analyse the data.

DISCUSSION

Dementia has been defined as a progressive impairment of intellectual and cognitive abilities brought on by neurological disorders[10]. Acetylcholinesterase inhibitors (AChEIs) have been studied in a number of controlled clinical trials using a selected population. For the treatment of dementia in patients with mild, moderate, and severe cases, the FDA has approved the drug donepezil[11]. Few studies on the effectiveness and safety of donepezil in dementia patients have been conducted in our region. Thus, the purpose of this study was to assess donepezil's effectiveness and safety in treating mild to moderate dementia.

MMSE was also significantly improved at the 20th week of treatment with donepezil (20.05±1.11) as compared to before treatment (15.05±3.49). This result was in agreement with the study of Abolfazli et al.[12]. In their study, the duration of the study period was 6 months. Six months after starting donepezil, the MMSE results of these patients revealed a statistically significant improvement (p=0.04).

This study revealed that the percentage increment of MMSE score was 6.29% at the 4th week and 35.04% at the 20th week of treatment with donepezil. The overall difference from baseline to end point of treatment was significant (p<0.001). Ishikawa et al. also observed similar findings in their study[13]. In a randomized, placebo-controlled trial, the percentage increment of MMSE score was significantly increased in dementia patients compared to the control group[14].

The well known side effects of donepezil include nausea, vomiting, diarrhoea, lack of appetite, dizziness, tiredness, weakness, difficulty in sleeping, tremors, and muscle cramps[15]. The present study revealed that the reported adverse effects at the 4th week of treatment were nausea (7.8%), vomiting (4.9%), diarrhoea (5.9%), and dizziness (6.9%). At the end of the 20th week, significantly fewer side effects had been reported.

It is thought that donepezil's primary pharmacological effects stem from the inhibition of this enzyme, which improves cholinergic transmission and reduces dementia symptoms[16]. Apart from the previously mentioned mechanisms, donepezil may also act by inhibiting glutamate induced excitatory transmission through down regulating N-methyl-D-aspartate (NMDA) receptors and regulating amyloid proteins, both of which have been shown to have a notable impact on the dementia process[17]. The suppression of several inflammatory signalling pathways, which has neuroprotective effects, may be another target for donepezil[18].

CONCLUSION

Donepezil's therapeutic dose is effective, well tolerated, and has no unexpected adverse effects in the treatment of mild to moderate dementia.

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