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EFFICACY OF MEMANTINE ON COGNITIVE FUNCTIONS OF PATIENTS WITH MODERATE VASCULAR DEMENTIA

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ABSTRACT

Introduction: Vascular dementia is a common condition for which there is no effective approved pharmacological treatment available. Absence of effective treatment creates a difficult situation for those suffering from the disease, their caregivers, and healthcare providers. The objective of this study is todetermine the Efficacy of Memantine on cognitive functions in patients with Moderate vascular dementia. **Material and methods:** This Case series study was carried out inthe Neurology Section of department of Medicine Ziauddin University and Hospitals North Nazimabad campus, Karachifrom 12th March 2010 to 11th March 2011.90 patients were included, who fulfilled the inclusion criteria after taking an informed consent. The SPSS version 11 was applied to the data. **Results:** There were 55 (59.1%) males and 38 (40.9%) females. Mean ± standard deviation age 69.7 ± 6.6 years, mean duration of symptoms was 1.76 ± 1.1 years. Baseline minimental examination score was 15.14 ± 3.1. Minimental score after 24 weeks of drug therapy was 17.14 ± 4.1. Efficiency was found in 62 (66.7%) patients. **Conclusion:** Memantine produced only a small benefit in cognition (of uncertain clinical significance) in patients with moderate vascular dementia. Data is insufficient to support widespread use of this drug in vascular dementia. Individual patient analysis is needed to identify subgroups of patients with vascular dementia who might benefit.

Key words: Vascular Dementia, Treatment, Memantine,

INTRODUCTION

Anticholinesterase and Memantine are Drugs, which specifically treat Alzheimers disease. Although these drugs do not halt the disease or reverse existing brain damage, they can improve symptoms and slow the progression of the disease[1]. Many researchers are also examining whether these drugs may be useful for treating other types of dementia [1-3].Improvement of dementia symptoms in clinical trials are assessed in 3 domains.
1. Cognitive end point, cognition is measured by objective test.
2. Functional end point, that is activity of daily living
3. Global end point, overall clinical response is measured by Global assessment. Minimental state examination (MMSE) is an objective Tool that is used for screening and measuring out come in cognition enhancing drug trials. It has a good sensitivity and specificity in detecting cognitive impairment with different dementia syndromes along with good concurrent validity when compared to verbal and performance intellectual quocient of the adult intelligence scale[5]. Some studies have confirmed the reliability and capacity of MMSE to measure cognitive improvement following treatment of depression[6] pooled trials of cholinesterase inhibitors identified an improvement of [1.4] point on MMSE over 6 months with simaltanous small but statistically significant improvements in daily life activity an behavioral symptoms[7]. Further moreSeveral previous studies have shown that Anticholinesterase can benefit patients with vascular dementia or concurrent Alzheimers disease and cerebrovascular disease. A 28 weeks,randomized placebo controlled trial on efficacy and tolerability of memantine in the treatment of mild to moderate vascular dementia has shown, improvement of 1.8 plus minus 3.51 points in cognition scale over base line score in 60% with memantine compared with 52% with placebo group, p=0.227[4]. As vascular dementia acounts for 15 to 20 percent of dementia cases worldwide and no effective treatment is available for it so, the aim of this study is to determine the effects of Memantine on cognitive functions of patients with vascular dementia. By knowing this we can prescribe drug to improve cognition in patients of vascular dementia. Therefore, our study will open new horizons in the era where dementia is considered untreatable . It will also be a positive addition to the available local data [9, 10]. So that it could be used in future, as there are only limited studies done on this topic.

MATERIAL AND METHODS

This Case series study was conducted inout patient department of Neurology Section, Department of Medi-

cine Ziauddin University and Hospital North Nazimabad campus, Karachi from 12th March 2010 to 11th March 2011. Sample size was calculated on the basis of proportion of previous studies, by using formula which includesp=60%,d=10%,1-alpha=95%,n=93 patients. Total 120 patients were enrolled, in order to compensate for dropouts,non probability purposive sampling technique was used. Inclusion criteria included patients of either gender of age being greater than 60 years, who fulfilled the DSMIV diagnostic criteria ofvascular dementia,and were graded as moderate vascular dementia on the basis of MMSE score ranging between [10-19] and with the duration of symptoms of more than 6 months.Patients with psychiatric illness ,history of stroke within prior 28 days or history of myocardial infarction were excluded from study. As these patients were deemed unable to make independent decision due to their decliningcognition, an informed consent was taken from their first kins and caregivers detailed explanation of the purpose of study, effects, side effects of the drug was provided. Patients were given Tab Memantine 10mg/day.then followed in out patient department by researcher herself for 6 months, at week [6, 12, 18] and [24]. The dose was stepwise escalated to 20 mg/day according to patients response (in terms of improvement in symptoms) till maximum tolerable gastrointestinal side effectsoccured. Minimental scoring was done after completion of 6 months of drug therapy and this information was entered in performa by the researcher. Improvement of >1 point from the baseline minimental score was labeled as efficacy positive. The data feeding and analysis was done on computer package SPSS (Statistical Package for Social Science) version 11.0. The results were computed as frequency and percentage for gender and efficacy, Mean and SD were used for age and duration of disease. Stratification was done with regared to age, gender and duration of disease to see the effect of these on the out come.

RESULTS

Ninety three patients fulfilling the inclusion criteria were included in this study. There were 55 (59.1%) males and 38 (40.9%) females (Figure I). Mean± standard deviation age 69.7 ± 6.6 years, mean duration of symptoms was 1.76 ± 1.1 years (Table I). Base line mini mental examination score was 15.14 ± 3.1 (Table I). Mini mental score after 24 weeks of drug therapy was 17.14 ± 4.1 (Table I). Symptomatic improvement was found in 62 (66.7 %) patients (Figure II). Mean age of male patients was 69 ± 6.3 years and mean age of female patients was 70.61 ± 7.0 years (Table II). Mean duration of male patients was 1.61 ± 0.99 years and mean duration of female patients was 1.97 ± 1.26 years. (Table II). Mean base line mini mental examination score of males was 15.33 ± 3.1 and mean base line mini mental of females was 4.87 ± 3.1 (Table II). Mini mental examination score after 24 weeks of drug therapy of males was 17.3 ± 4.2 and mini mental examination score after 24 weeks of drug therapy of females was 16.95 ± 3.94 (Table II). Mean age of patient in whom drug was effective was 69.7 ± 6.8 years, mean duration of symptoms 1.7 ± 1.1 years, mean base line mini mental examination score was 15.6 ± 3 and mini mental examination score after 24 weeks of drug therapy was 17.13 ± 4.09 (Table III).

TABLE I ANALYSIS OF DESCRIPTIVE STATISTICS

Variable	Minimum	Maximum	Mean	Std. Deviation
Age/years	61	87	69.7	6.6
Duration of symptoms	1	6	1.8	1.1
Baseline minimental examination score	9	19	15.1	3.1
Minimental examination score after 24 weeks of drug therapy	8	29	17.1	4.1

TABLE II ANALYSIS OF DESCRIPTIVE STATISTICS AMONG THE GENDER

Gender		Age	Duration of symptoms	Baseline minimental examination score	Minimental examination score after 24 weeks of drug therapy
Male	Mean	69	1.6	15.3	17.3
	SD	6.3	1	3.1	4.2
Female	Mean	70.6	2	14.9	16.9
	SD	7	1.3	3.1	3.9
p value		0.483	0.040	0.266	0.696

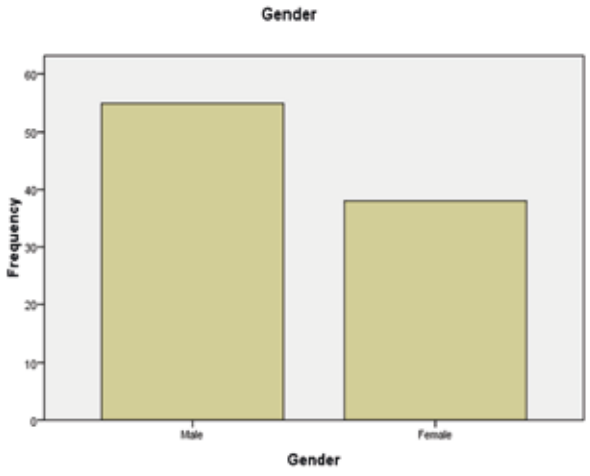
TABLE III ANALYSIS OF DESCRIPTIVE STATISTICS AMONG THE EFFICACY

Symptomatic improvement		Age	Duration of symptoms	Baseline minimental examination score	Minimental examination score after 24 weeks of drug therapy
Yes	Mean	69.7	1.7	15.6	18.1
	SD	6.8	1.1	3	3.7
No	Mean	69.7	1.8	14.2	15.3
	SD	6.4	1.2	4	4.2
p value		0.808	0.775	0.002	0.057

DISCUSSION

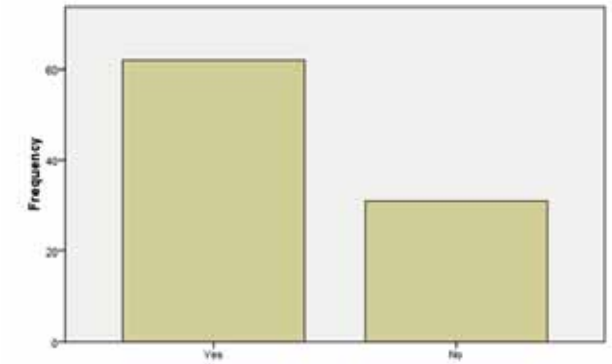
Vascular dementia is the second most common cause of dementia after Alzheimers disease in aging population [9]. It is a heterogenous condition including single large infarct,multiple small infarcts along with diffuse whitematter ischemic lesions [12]. It is evident that stroke risk factors such as Hypertension, Diabetesmelitis, Myocardialinfarction and Smoking have a contributory effect on Alzheimers disease and there is also an overlap in pathphysiology of both Alzheimers and vascular dementia [13, 14]. Memantine produces its effect by being aN methyl D Aspartate receptor antagonist. Since NMDA Receptor mediated excitotoxic nerve cell death, is considered to be of paramount importance in ischemic cell death. It is alsoneuroprotectiveand consider potentialy therapeutic in many neuropsychiatric diseases as well[15].

FIGURE I ANALYSIS OF GENDER



It has been approved by FDA as monotherpy and in combination with anticholinesterase for moderate to severe Alzeimers disease. On the basis of overlap in pathophsiology of Alzheimers disease and vascular dementia,its considered quite promising to use Memantinefor later. A 28 weeks placebo based triall tested Memantinein dose of 20 mg/day dose.Data analysis showed significant improvement in cognitive functions from baseline over placebo with no change inclinical global scale [16]. An other pooled analysis of 6 months clinical trial showed cognitive improvement (using the ADAD-cog). patientswho receivedMemantine, had statistically significant better outcome and mild adverse effects.[17]. A study of Memantine/chEI combination therapy had similar results and Conclusion[18]. On basis of these studies one can conclude that memantine has a potential to treat vascular dementia but at the same time they also indicate that there is in- adequate data available in this regard and further studies are needed to consider.

FIGURE II ANALYSIS OF SYMPTOMATIC IMPROVEMENT
SYMPTOMATIC IMPROVEMENT



In our study we did not find statistically significant improvement in cognitive function of patients with moderate vascular dementia. On further review of literature it has been observed that there are relatively few studies on the treatment of vascular dementia with several compounds of different mechanism of actions that showed mild efficiency in cognitive functions of these patients.So probably its not only cytotoxic cell death, but a number of other different mechanisms which play role in etiopathgenesis of vascular dementia.Micro array analysis of messenger RNA for monitoring of behavior of large number of genes may also reveal complex cascade of reactions for regulation of nerve cell susceptibility to injury[19]. In future otherneuroprotective drugs with simultaneous targeting effects on multiple events related to cell death and

certain transcription related genes are expected to be very effective in treatment of vascular dementia.

CONCLUSION

Memantine produces small benefits in cognition of uncertain clinical significance in patients with mild to moderate vascular dementia. Data is insufficient to support widespread use of this drugs in vascular dementia. Individual patient analysis is needed to identify subgroups of patients with vascular dementia who might benefit from it.

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Author's contribution:

Dr. Saima Nazish: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Dr. Bashir A Soomro: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Dr. Shafaqalvi: Data collection, data analysis, manuscript writing, manuscript review