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Efficacy and safety of MAO-B inhibitor versus donepezil in Chinese elderly stroke patients with Alzheimer disease: A potential therapeutic option

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Abstract: This pilot study designed to evaluate the efficacy and safety of MAO-B inhibitor in comparison with Donepezil (DNP) in elderly Chinese patients with Alzheimer disease (AD). In the present clinical trial, Chinese elderly patients aged ≥65 years with a confirmed diagnosis of AD were enrolled. The patients received MAO-B inhibitor (Selegiline 5 mg) or DNP 10 mg daily (reference) for 6 months. The efficacy and safety data were collected from 120 patients (60 patients in each group) every 3 weeks until 6 months. The primary endpoints were to assess the change in cognitive score from baseline in both the treatment group. The result of the present study showed that the patients treated with MAO-B inhibitor and DNP have similar efficacy and safety profile Considering the clinical benefit, mean (SD) improvement in sign and symptoms was numerically greater in DNP-treated patients as compared to MAO-B inhibitor at endpoint visit (SIB: 12.3 (3.7) vs 11.3 (4.2); AD severity: 14.2 (3.5); CIBIS+/CIBIC: 10.2 (2.7) vs 9.4 (3.2); ADCS-ADL: 14.3 (4.2) vs 13.2 (3.4); MMSE: 14.3 (3.7) vs 12.2 (3.2), P>0.05 respectively for each comparison). However, a statistical difference in terms of clinical benefit was similar between both the treatment groups (p>0.05). Overall, both the study drugs were found comparable in relieving the symptoms of AD (severity score after end of treatment: 14.2 vs 13.4 respectively; p >0.05). This indicates that MAO-B inhibitor is a potential target for the treatment of AD in China. The results of the present study may help to design a large clinical trial to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in AD patients.

Keywords: Selective MAO-B inhibitor, donepezil, post-stroke cognitive impairment, selegiline.

INTRODUCTION

Alzheimer disease (AD) is a progressive degenerative disease related to advanced cognitive deterioration and dementia. Cognitive capability becomes gradually compromised in patients with progressive AD. Currently approved treatments for AD are mainly symptomatic, and neither slows the progression of the disease nor prevents neurological degeneration (WHO, 2015). It is estimated that currently more than 46 million people worldwide live with dementia, and by the year 2050, the number of people with dementia will reach 131.5 million. With the rapidly increasing number of elderly people with dementia in China, it is very important to know the root cause of developing AD in healthy subjects (Guzior, 2015; Cummings, 2017). Currently, there are several approved treatment modalities are available for managing AD worldwide, such as AChEIs that includes donepezil, galantamine, rivastigmine, and NMDA receptor blockers, which have reported to improve the symptoms of AD, however no curative treatment available (Harvey, 2018; Reddy, 2019; O'Brien, 2017). Globally, stroke is the 2nd most common reason of mortality and disability among elderly patients (Rothenburg, 2010; Drake, 2011; Maier, 1998). Role of stroke in cognitive deficit is well documented in several reports, accounts for up to 80% cases of PSCI (Post stroke cognitive impairment) (Rothenburg, 2010; Drake, 2011; Maier, 1998). The primary mechanism of PSCI is not known comprehensively (Drake, 2011; Maier, 1998).

The expression of monoamine oxidase enzyme has been significantly increased in patients with cognitive disorder such as AD and PSCI (Shih, 2018; Schedin-Weiss, 2017; Alam, 2019). Among both type of MAO enzymes, the expression of MAO- B enzyme was higher in hippocampus and cortex area of brain as compared other MAO–A enzyme. In patients with cognitive deficit, the expression of MAO-B was approx. 60% higher in hippocampus and cortex area of brain region; this indicates over activity of MAO B enzymes in cognitive disorder. Several studies showed the involvement of MAO-B enzyme in pathological progression of neurodenerative disorders, and reports suggested the involvement of oxidative stress, which is the primary cause of neurodegenerative processes in cognitive disorder (Nakamura, 1990; Saura, 1994; Riederer, 2004; Schedin-Weiss, 2017; Roth BL, 2004). MAO-B enzymes metabolized to monoamines such as dopamine and serotonin, and over activation of MAO-B enzymes results in decreased level of dopamine and serotonin which have been reported in cognitive disorder such as Alzheimer's disease (Mitchell, 2011). Therefore, MAO-B inhibitor could be a potential therapeutic option in treating

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cognitive disorder. Donepezil is a short acting acetylcholinesterase inhibitor and has ability to improve cholinergic transmission in CNS (Feldman, 2001; Winblad, 2006). Donepezil in its approved dose of 5-10 mg per day after 6 months of treatment was associated with significant improvement in memory.

The functional role of MAO-B inhibitor in patients with AD was not evaluated in Chinese individuals. There is no clinical trial which evaluates the efficacy of and safety MAO-B inhibitor in patients with AD in comparison with the standard therapy such AChEI (such as DNP). This is a first clinical trial which compares the efficacy and safety of MAO-B inhibitor with DNP in patients with AD. We, therefore, designed this pilot study to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in elderly Chinese patients with AD. Our study may help to design a large clinical trial to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in AD patients of other countries. We hypothesize that MAO-B inhibitor would improve the transmission of cholinergic receptor and thereby improve the cognitive function among the AD patients. We, thus, designed this pilot study to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in elderly Chinese patients with AD.

MATERIALS AND METHODS

Patients and ethics

In the present clinical trial, Chinese elderly patients with aged ≥65 years with a confirmed diagnosis of AD was explained the study protocol and methodology and then enrolled at Huai'an Hospital of Xuzhou Medical University, China after getting their written informed consent form. Study design and inform consent form and other study-related documents including protocol were submitted in an ethical committee for review and approval. The study was conducted after getting written approval from the ethics committee vide ethics committee approval number: IRB/XMU-4/EC-231/12/18. All the enrolled subjects underwent laboratory examination to authorize their suitability for this study.

Patients with any other neurodegenerative disorder were excluded from the trial. Also, patients with hypersensitivity to any of the study products will be excluded. Hypersensitivity of study product was ruled out using patients past history during the screening visit. Also, the patients with dementia due to cerebrovascular or Huntington's disease was excluded from the trial. Also, patients with any other pathology, which investigator feels may harm or confound the results of the study will be excluded. Also, the patients taking concomitant medicines were recorded. The patient who can't discontinue the concomitant medication which may affect the efficacy and safety of study drugs were excluded.

Design

The enrolled patients who satisfied all the eligibility criteria were equally randomized in two groups in the allocation ratio of 1:1. The patients in the test group were received MAO-B inhibitor (5 mg twice daily), and the subjects who were in the active comparator group received DNP 10 mg daily for 6 months. In the MAO-B inhibitor group, subjects received selegiline for 6 months. After treatment, the efficacy and safety data were collected at every 3 weeks to 6 months. The primary endpoints were to assess the change in cognitive score from baseline in both the treatment group using the SIB scale. Also, each enrolled patients was interviewed to assess the functional status using the CIBIC scale. SIB scale is forty item scales, with score ranged from 0 (severely affected) to 100 (least affected) was subjected to each patient. The CIBIC scale recorded data from the patients and their caregiver on a seven-point scale (low score denotes improvements, where a high score indicates low improvements leading to worsening of symptoms). The CIBIC scale has used a baseline score of patients and caregiver as a reference, and change from baseline at each follow-up visit was calculated. Also, the ADCS-ADL scale was used to evaluate daily living score to assess whether there was any notable benefit among the patients after treatment or not. Also, the cognitive function of each subject was tested using the MMSE scale, which ranges from 0 to 54, where 0 indicates that severely impaired or severely affected, and 54 indicates least affected/impaired. All the scales were subjected by trained staff and were the blind observer. Safety data were also assessed. Also expression of MAO B enzyme assed using PET imaging in AD patients before and after treatment was evaluated.

STATISTICAL ANALYSIS

Since the present study was intended as a pilot trial study to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in elderly Chinese patients with AD. Thus, no formal sample size calculation was accomplished. The present pilot trial planned to enroll at least 50 AD patients in each treatment group. Our study may help to design a large clinical trial to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in AD patients of other countries. Numerical data were analyzed using Mann Whitney or unpaired t-test after subjecting data into normality analysis. Based on the result of normality, appropriate test either unpaired or Mann Whitney test was applied to find p-value between both the treatments. Numerical data were presented using Mean (SD). Categorical data were analyzed using Fisher exact test or chi-square test based on the number of data in each row/column and data were presented using an absolute number or % of patients. A p-value of less than 0.05 was considered a statistically significant between both the study drugs. The current hypothesis was that

MAO-B inhibitor is non-inferior to DNP in AD patients. Graph Pad Prism latest version was used statistical analysis of data.

RESULTS

A total of 150 patients were screened for the present study, of those 120 AD patients who met eligibility criteria were recruited at the Huai'an Hospital of Xuzhou Medical University, China. All 120 patients who were recruited have completed the study period of 6 months. Data were analyzed, and results pertaining to demography and baseline characteristics were compared and found that there was no significant difference between both the treatment groups. Demography and baseline characteristic was found similar between both the treatment groups (table 1).

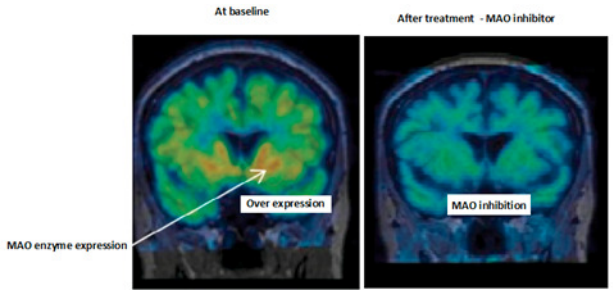

Fig. 1: Imaging results showing expression of MAO B enzyme in AD patients before and after treatment of Selegiline

Expression of MAO B enzyme in AD patients before and after treatment of Selegiline shown in fig. 1. Imaging results showed that there was significant reduction in expression of MAO B enzyme in AD patients treated with Selegiline (fig. 1).

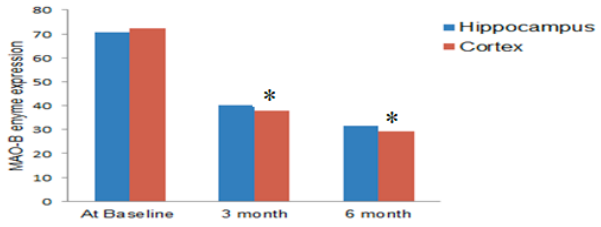

Fig. 2: Expression of MAO B enzyme in AD patients before and after treatment of Selegiline.

Moreover, MAO enzyme activity status in two prominent brain regions involved in learning and memory was also investigated, namely hippocampus and cortex. At baseline, PET results showed that there was significant expression of MAO B enzyme in hippocampus and cortex brain region of AD patients. After treatment with MAO-B inhibitor, PET results showed that there was significant reduction of expression of MAO B enzyme in hippocampus and cortex brain region of AD patients treated with Selegiline (fig. 2).

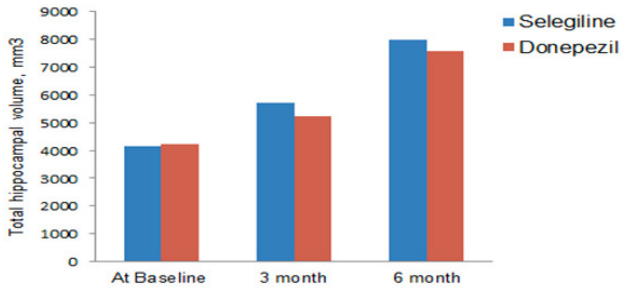

Fig. 3: Total hippocampal volume in AD patients after treatment of Selegiline and donepezil

After treatment at each visit, SIB score at baseline was similar in AD patients of both the groups. Change in SIB score from baseline was statistically similar in both the treatment group; however, the SIB score was numerically greater in patients who received standard therapy (DNP) as compared to MAO-B inhibitor. The severity of AD signs and symptoms were similar at the baseline visit, however, the difference was not statistically significant between both the treatment groups and however, DNP-treated patients had numerically greater relief in signs and symptoms of AD as compared to the patients treated with MAO-B inhibitor. A similar trend of results was found for CIBIC scale results. The severity of functional status was similar at the baseline visit, however, the difference was not statistically significant between both the treatment groups and however, DNP-treated patients had numerically greater relief in signs and symptoms of AD as compared to the patients treated with MAO-B inhibitor (table 2). Also, the ADCS-ADL scale which was used to evaluate daily living score showed a similar trend of results, favoring both the study treatments. However, improvement in daily living scores was numerically greater in patients treated with DNP as compared to MAO-B inhibitor. However, the difference in daily living scores after both the treatment at every visit till 6 months, showed no statistically significant difference between both the treatments. However, numerically trend of data showed that patient treated with DNP had numerically greater improvement in daily living scores as compared to the patients treated with MAO-B inhibitor. A similar trend of results for the cognitive function was noted and showed that difference between both the treatment groups was not statistically significant; however, DNP-treated patients had numerically greater relief in signs and symptoms of AD as compared to the patients treated with MAO-B inhibitor (table 2).

At baseline, hippocampus volume in AD patients was low in both the treatment group. Improvement in hippocampus volume was significant in both the treatment group as compared to baseline (fig. 3). The improvement was numerically greater in patients treated with donepezil as compared to Selegiline. However, the difference was not statistically significant between both the treatment groups.

The most common adverse drug reaction (ADR) in both the treatment group were nausea, diarrhea, hypotension, and bradycardia. The incidence of adverse events (AEs) was comparable in both the group, however, numerically; it was greater among patients treated with DNP as compared to the incidence rate of MAO-B inhibitor. Both the treatments were found to have acceptable safety profile and tolerability. The most common AEs observed in both the treatment groups were nausea, diarrhea, hypotension, and bradycardia (table 2).

Table 1: Demography and baseline characteristic of enrolled Chinese patients with AD

Characteristics	Selegiline N=60	Donepezil N=60
Age, mean (SD)	63.4 (4.2)	61.5 (3.2)
Gender (Male/female, %)	45/55	52/48
Weight, mean (SD)	72 (3.5)	71 (5.5)
Body mass index, mean (SD)	26 (1.4)	25 (2.4)
MoCA score (SD)	23.8 (1.8)	24.8 (1.3)
Baseline computerized total cognitive score (SD)	87.8 (1.8)	24.8 (1.3)
Patients with cognitive impairment (mild to moderate), %	23 (46%)	21 (42%)
Total hippocampal volume, mm3 (SD)	4134 (231)	4214 (341)
MAO-B expression, %	71.2	72.2
Baseline score		
SIB, mean (SD)	56 (2.3)	52 (3.5)
CIBIS+/CIBIC, mean (SD)	64 (3.1)	59 (2.1)
ADCS-ADL, mean (SD)	69 (4.4)	63 (3.5)
MMSE, mean (SD)	62 (3.1)	65 (4.1)
Mental illness status		
Mild	10	7
Moderate	28	21
Severe	12	22
Living status		
Living with friend	20	21
Living with caregiver	22	19
Living with relative or friend	18	10

Table 2: Effectiveness of donepezil or MAO-B inhibitor in patients with moderate to severe Alzheimer's disease

Variable	DNP group N=60	MAO-B inhibitor* N=60
SIB		
Baseline	71.4	66.2
At follow visit	61.6	57.4
At endpoint	12.3	11.3
AD severity		
Baseline	68.2	67.4
At follow visit	57.1	56.1
At endpoint	14.2	13.4
CIBIS+/CIBIC		
Baseline	65.3	63.4
At follow visit	55.2	54.7
At endpoint	10.2	9.4
ADCS-ADL		
Baseline	76.7	73.3
At follow visit	64.3	62.8
At endpoint	14.3	13.2
MMSE		
Baseline	75.4	71.1
At follow visit	63.4	59.1
At endpoint	14.3	12.2

*Non-significant difference between both the groups.

Table 3: Summary of ADR in patients treated with donepezil or MAO-B inhibitor in patients with Alzheimer's disease

ADR type	DNP group N=60	MAO-B inhibitor N=60
Non-Serious AEs, %		
Nausea	21	19
Diarrhea	41	37
Hypotension	21	16
Bradycardia	14	11
Contusion	11	8
Dizziness	7	4
Diarrhea	5.3	3.3
Serious AEs		
Pneumonia	3	2
Confusional condition	2	1

None of patients experienced life-threading or fatal adverse events in either group of treatment. There were few patients who experienced serious adverse events is summarized in table 2.

DISCUSSION

This was the first study designed to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in elderly Chinese patients with AD. The result of the present study showed that the patients treated with DNP and MAO-B inhibitor have similar efficacy and safety profile. Although, considering the clinical benefit, improvement in sign and symptoms of was numerically greater in DNP-treated patients as compared to MAO-B inhibitor. However, a statistical difference in terms of clinical benefit was not present between both the treatment groups. Thus, overall, both the study drugs were found comparable in relieving the symptoms of AD. Our study results pertaining to DNP was consistent with other reported published studies (Harvey, 2018; Reddy, 2019; O'Brien, 2017). The results of the present study may help to design a large clinical trial to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in AD patients of other countries.

This was the first study to suggest the role of MAO-B inhibitor in Chinese patients with AD. The present results showed attractive results for MAO-B inhibitor in the management of AD. The present study suggests targeting to monoaminergic pathway to find better treatment modalities for the management of AD. Our finding in the present study supports the finding of previously published studies that the inhibition of MAO expression improves the signaling pathways of dopaminergic and serotonergic in cortical regions and the hippocampus region of the rat's brain (Shih, 2018; Schedin-Weiss, 2017; Alam, 2019). This could be the reason for the positive results of MAO-B inhibitor in Chinese patients with AD. Moreover, the results of pre-clinical studies show activation of dopaminergic and serotonergic pathways in the central nervous system, especially in the hippocampus and cortical region, which lead to increased signaling transmission of cholinergic receptors, which may results in increased level acetylcholine in hippocampus and cortical region (LStrosznajder, 2005; Adamczyk, 2005; Shaw, 2002). Decreased transmission of cholinergic receptors and acetylcholine was found in AD, which is well known pathological characteristic of AD. This indicates that MAO-B inhibitor is a potential target for the treatment of AD in China. Also, our study results are consistent with the previous reports suggesting NMADA receptor blockers improve cognitive functions by increasing the signaling transmission of dopaminergic and serotonergic in cortical regions and the hippocampus region. This indicates the increasing dopaminergic and serotonergic transmission in brain regions would be helpful in improving the cognitive functions in AD. This could be a novel treatment option for effective therapy in patients with AD. The present study results showed that MAO-B inhibitor would improve the transmission of cholinergic receptor and thereby improve the cognitive function among the AD patients. Our study may help to design a large clinical trial to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in AD patients of other countries. We encourage to conduct multi-centric studies in China and globally to generalize this finding.

CONCLUSION

This was the first study to suggest that the patients treated with DNP and MAO-B inhibitor have similar efficacy and safety profile. Although, considering the clinical benefit, improvement in sign and symptoms of was numerically greater in DNP-treated patients as compared to MAO-B inhibitor. However, both the study drugs were found comparable in relieving the symptoms of AD. This indicates that MAO-B inhibitor is a potential therapeutic option for the treatment of AD in China. The results of the

present study may help to design a large clinical trial to evaluate the efficacy and safety of MAO-B inhibitor in comparison with DNP in AD patients of other countries.

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