Original Article

Sensitivity of Montreal Cognitive Assessment in Comparison with Mini Mental Status Examination in Testing Cognitive Status in Epilepsy Patients with Phenytoin Monotherapy

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ABSTRACT

Background and objective: Most studies follow Mini Mental Status Examination (MMSE) to assess cognitive status in epilepsy population with phenytoin monotherapy, however its sensitivity on detecting cognition in this population remains debatable. Previous study observed Montreal Cognitive Assessment (MOCA) being more sensitive in testing cognitive status in patients with stroke, parkinsonism, cardiovascular events, epilepsy etc. Therefore, in the present study, we examined the sensitivity of MOCA compared with MMSE in testing the cognitive status in epilepsy population with phenytoin monotherapy.
Method: This case-control study enrolled 63 newly diagnosed epilepsy patients (controls) and 60 epilepsy patients with phenytoin monotherapy up to one year. Both controls and cases were screened using MMSE and MOCA for cognitive function.
Results: MOCA showed cognitive impairment 70% in controls and 100% in cases as compared to 12% in controls and 94% in cases with MMSE. Our findings indicate that MOCA could detect cognitive impairment that failed with MMSE in both controls and cases, possibly the MOCA subscales contributed to contributed to higher sensitivity of MOCA as compared to MMSE.
Conclusion: MOCA was found to be more sensitive and reliable than MMSE in testing the cognitive status in epilepsy population with phenytoin monotherapy.

Keywords: Cognitive impairment, Epilepsy, MMSE, MOCA, Phenytoin.

INTRODUCTION

Epilepsy is a common episodic neurological condition characterized by seizures and is currently managed with first generation or second generation anti epileptic drugs (AEDs). Although phenytoin, carbamazepine and valproic acid remain the drugs of choice among the first generation AEDs, their adverse reactions remain a concern for effective management of epilepsy. Hypersensitivity syndrome and central nervous system (CNS) adverse effects particularly cognitive impairment are more commonly noticed adverse reactions with first generation AEDs the severity of these adverse reactions partly correlate with the duration of treatment with these drugs.[1] Other factors such as the control of epilepsy and dose of AEDs are also reported playing a role in influencing these adverse effects.[2,3] Phenytoin remains the most commonly used drug among the first generation AEDs for all types of epilepsy seizures.

However, cognitive impairment is common with phenytoin monotherapy and is considered as a feared consequence as it directly affects the quality of life.[4] And is considered as a feared consequence of phenytoin monotherapy among the CNS adverse effects.[5] Therefore, accurate diagnosis of cognitive impairment is of prime importance in epilepsy population.

Now a days cognitive impairment is assessed by using Mini Mental Status Examination (MMSE). MMSE is a brief mental status test measuring orientation, concentration, immediate and delayed memory, language and constructional praxis.[6] Until 2001, no instruments were available to detect mild cognitive impairment (MCI). MMSE, though useful, showed cognitive score in the normal range in most subjects as it has low sensitivity to detect MCI. So far, the cognitive function was assessed using MMSE which was found to be insensitive at detecting cognitive impairment.[8]

So, in cases where MMSE score is shown in the normal range (24 to 30) and there is suspicion of cognitive status, the subjects could be screened with Montreal Cognitive Assessment (MOCA). MOCA is a 30-point scale with seven cognitive subtests including visuospatial/executive functions which are not found in MMSE. This would help to demonstrate objective cognitive loss.[9] MOCA is feasible and superior to the MMSE in screening for cognitive impairment in sub acute stroke/transient ischemic attack patients, as it detects complex cognitive impairments such as executive function, visual perception and construction.[10] MOCA is more sensitive to changes in types of dementia that particularly affect the frontal lobe because of its emphasis on tasks of frontal executive functioning, compared with the MMSE and therefore MOCA is a useful additional screening for individuals in a memory clinic setting who score over 25 points on the MMSE.[11] In cryptogenic epilepsy patients who reported normal cognition on MMSE, MOCA showed cognitive impairment in these patients and thus suggesting MOCA as a screening tool for patients with epilepsy.[12]

Based on the above considerations, the present study aimed to investigate the sensitivity of MOCA in comparision with MMSE in detecting cognitive status in epilepsy patients with phenytoin treatment.

METHODS

One hundred and twenty three epilepsy patients (≥18 years old) admitted to the neurology department at Shri Preethe Neuro Hospital, India. Ethical approval was granted by the Institutional Ethics Committee, Swamy Vivekanandha College of Pharmacy, Tiruchengode, India. The study population was well informed about the study by providing patient information form and the consent was obtained in patient consent form before included in the study. The patient information and consent form were prepared in English and local language (Tamil) as per the Indian Council of Medical Research (ICMR) guidelines before start of the study. Sixty three newly diagnosed generalized tonic-clonic epilepsy patients who reported to the study site within 24 hours of last seizure with abnormal EEG and normal CT and never had treatment with AEDs were considered as control group. Sixty epilepsy patients who were treated with phenytoin monotherapy for one year and showed the serum drug concentration within therapeutic range (10 to 20 µgm/ml), with normal EEG and CT and free from seizure for the last three months were considered as cases group.

Demographics and clinical profile

Basic demographic information including age, gender, and level of education were collected.

Mini Mental State Exam (MMSE)

Folstein's Mini Mental State Exam Form was used in the study. Any score greater than or equal to 25 points (out of 30) is normal. Below this score show mild (21-24 points), moderate (10-20 points) and severe (≤9 points) cognitive impairment.[6,13,14]

Montreal cognitive assessment scale (MOCA)

MOCA scale was also used to monitor different cognitive domains. A cut-off score ≥ 26 is considered normal, <26 is mild cognitive impairment.[15,16]

Serum phenytoin concentration

Serum phenytoin concentration was assessed by using Fluorescent Polarization Immunoassay (FPIA) method (Abbott AxSYM System, Mumbai, India).[17]

Statistical analysis

Chi-square analysis was carried out to analyze the demographics of the study population with respect to control and cases. Differences between the mean ± SD of two groups (cases and controls) were analyzed by the two-tailed unpaired Student's t test and differences between median analyzed by Mann-Whitney test. One way Analysis of Variance (ANOVA) with Tukey's pairwise comparison procedure were used for the comparison of parameters among groups of the study. Graph pad in stat prism 4.0 software package was used in the statistical analysis.

RESULTS

Cognitive status in demographics of the study population

Controls and cases (Table 1) did not show significant difference in their demographics with regard to age ($\chi 2$=0.735; P=0.391), gender ($\chi 2$=1.449; P=0.228) and educational status ($\chi 2$=0.296; P=0.585). No significant difference was observed between cognitive status, age and educational status of the controls as well as cases either with MMSE or MOCA screening; while there was no significant difference in cognitive score between male and female in controls with MMSE and MOCA showed significantly lower cognitive score in female when compared with that in male (P<0.05)

in the same population. Among the cases, female showed significantly lower cognitive score as compared to male with both MMSE and MOCA (P<0.05).

On comparison between MMSE and MOCA, MOCA showed significantly lower cognitive score (P<0.05) as compared to that with MMSE in both male and female of the study population. Overall, the cognitive scores with MOCA were significantly lower than that of MMSE (P<0.05) in demographics of both controls and cases. (Table 2).

Comparison between MMSE and MOCA on different cognitive status of controls and cases

The cognitive status of controls and cases were compared between MMSE and MOCA (Table 3). MOCA showed higher number of patients with mild cognitive impairment as compared to MMSE in controls. While MOCA identified 69.85% of patients with mild cognitive impairment in controls, MMSE able to detect only 9.52% mild cognitive impairment and 3.17% of moderate cognitive impairment in the same population. In cases too, MOCA showed all patients with mild cognitive impairment; however MMSE reported 5% with normal cognitive score with remaining cases showing mild to moderate cognitive impairment. In controls as well as cases significant differences (P<0.05) in cognitive scores were observed between MMSE and MOCA. Significant difference (P<0.05) in cognitive score was observed between controls and cases on both MMSE and MOCA.

MMSE Vs. MOCA on association between phenytoin concentration and cognitive status in cases

Linear regression analysis of the data did not show any correlation of phenytoin concentration with cognitive status on both MMSE and MOCA in the study population with phenytoin monotherapy (Table 4).

DISCUSSION

The present study clearly demonstrated the sensitivity of MOCA over MMSE towards the detection of cognitive impairment in both controls and cases. Significant difference (P<0.05) in cognitive score was observed between MMSE and MOCA in the epilepsy population in the present study thus supporting the earlier contention that the prevalence of MCI and associated patient correlated factors might be increased according to MOCA despite normal MMSE score and the cognitive impairment might occur in a range of domains of the MOCA.[17] The usefulness of MOCA over MMSE in the assessment of cognitive status is well established in parkinsonism,[18] stroke,[10] and cryptogenic epilepsy.[12] Furthermore, cognitive impairment is most common in epilepsy patients receiving phenytoin monotherapy and therefore warrants a sensitive and reliable method that can accurately diagnose cognitive status in this population. Towards this objective the present study aimed to test the sensitivity of MOCA as compared to MMSE in assessing cognitive status in patients receiving phenytoin monotherapy. In the present study, both controls and cases were carefully selected based on EEG abnormalities and CT scan in accordance with the prescribed norms for identifying epileptic population and also in accordance with some previous study.[19]

Neither MMSE nor MOCA could make differences in cognitive status in age and educational status of the study population; however, significant differences in cognitive scores were observed between male and female in controls as well as cases with both MOCA and MMSE. Cognitive scores were significantly lower (P<0.05) in female as compared to male, possibly the

circulating androgens in male play important modulatory role in neuro degenerative disorders and thus protect cognitive function.[19] MOCA identified mild cognitive impairment (<26) in female among the controls which was not detected by MMSE. According to MOCA, all cases reported mild cognitive impairment (<26). On the contrary, MMSE failed to detect cognitive impairment among the cases as 5% of them reported normal (>24). These findings point to suggest the poor sensitivity of MMSE in assessing cognitive status in epilepsy patients with phenytoin monotherapy. The poor performance of the MMSE in detecting cognitive impairment in cases may be due to several factors. The MMSE is less capable of testing for complex cognitive impairments in domains such as visuospatial, executive function and abstract reasoning. In addition, the MMSE subtests of Attention and Delayed Recall contain test items which are not as challenging as contained in the MOCA.[20] Therefore early detection of cognitive impairment by MOCA screening may help clinicians to intervene and improve prognosis in epilepsy patients with phenytoin monotherapy. The results from the present study indicate that both cases and controls were found to have significantly greater decline in cognitive score by MOCA screening and moreover cognitive status in cases was found to be poorer by MOCA screening rather than by MMSE screening. No correlation was observed between phenytoin concentration and cognitive status in cases on both MMSE and MOCA and our finding is consistent with earlier observation.[21]

Therefore, MOCA could detect mild cognitive impairment among the controls, which MMSE failed to detect. Moreover, MOCA could help detect cognitive impairment in patients with phenytoin monotherapy which was otherwise undetectable on MMSE.

CONCLUSION

The results of the present study demonstrate that MOCA is more reliable than MMSE in testing cognitive status in epilepsy population with phenytoin monotherapy. Although MMSE remains the gold standard for assessing cognition in epilepsy population the usefulness and reliability of MOCA in detecting cognition in this population cannot be underestimated and therefore our findings propose MOCA in preference to MMSE as a screening tool for assessing cognitive status accurately in epilepsy patients receiving phenytoin monotherapy.

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REFERENCES

1. Schlienger RG, Shear NH. Antiepileptic drug hypersensitivity syndrome. *Epilepsia* 1998; 39:S3–S7.
2. Reynolds EH. Phenytoin: toxicity. In: Levy R, Mattson RH, Meldrum B, Penry JK, Drefuss FE. editors. Antiepileptic drugs, New York: Raven Press. (1989).
3. Butlin AT, Danta G, Cook ML. Anticonvulsants, folic acid and memory dysfunction in epilepsys. *Clinl Exp Neurol* 1985; 20:57-62.
4. Gilliam F. Optimizing health outcomes in active epilepsy. *Neurology* 2002; 58:S9–S20.
5. Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures, Effects on intelligence and on seizure recurrence. *N Engl J Med* 1990; 322:364-9.
6. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for

grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; I2:189-98.
7. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Med* 2004; 256:183–94.
8. Nys GM, Van Zandvoort MJ, de Kort PL, Jansen BP, Kappelle LJ, de Haan EH. Restrictions of the Mini-Mental State Examination in acute stroke. *Arch Clin Neuropsych* 2005; 20:623–9.
9. Howard C, Ziad N, Yves J, Valerie D, John K, Fadi M, Sylvie B, Howard B. Mild cognitive impairment and cognitive impairment, no dementia: Part A, concept and diagnosis. *Alzheimer's & Dementia* 2007; 3:266–82.
10. YanHong D, Vijay KS, Bernard PC, Narayanaswamy V, Hock LT, Raymond CSS, Sophia T, Yiong HC, Christopher C. The Montreal Cognitive Assessment (MOCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. *J Neurol Sci* 2010; 299: 15–8.
11. Tasha S, Nadia G, Clive H. The Montreal Cognitive Assessment: Validity and Utility in a Memory Clinic Setting. *Can J Psychiatry* 2007; 52:329-32.
12. Phabphal K, Kanjanasatien J. Montreal Cognitive Assessment in cryptogenic epilepsy patients with normal Mini-Mental State Examination scores. *Epileptic Disord* 2011; 13:375-81.
13. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. *JAMA* 1993; 269:2386-91.
14. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc* 1992; 40:922-35.
15. Nasreddine ZS, Phillips NA, Bdirian V. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005; 53:695–9.
16. Nazem S, Siderowf AD, Duda JE, Have TT, Colcher A, Horn SS, *et al*. Montreal cognitive assessment performance in patients with Parkinson's disease with "normal" global cognition according to mini-mental state examination score. *J Am Geriatr Soc* 2009; 57:304-8.
17. Lu-Steffes M, Jolley M, Pittluck G, Panas H. Fluorescence polarization immunoassays of Phenytoin and Phenobarbital. *Clin Chem* 1981; 27:1093.
18. Timothy P. Angela R, Reid O, Cara P, Jacob A. Role of circulating androgens levels in effects of apoE4 on cognitive function. *Brain Res* 2005; 1053:88-96.
19. Palanisamy A, Rajendran NN, Narmadha MP, Ganesvaran R. Association of apolipoprotein E ε4 allele with cognitive impairment in epilepsy. *Epi and Behav* 2013; 26:165-9.
20. Ihl R, Frolich TD, Martin EM. Differential validity of psychometric tests in dementia of Alzheimer type. *Psychiatric Res* 1992; 44:93–106.
21. Jan V, Albert PA. Cognitive side effects of chronic antiepileptic drug treatment: A review of 25 years of research. *Epilpsy Res* 1995; 22:65-95.

Table 1. Demographics of the study population (n=123)

Variable	Controls (n=63)	Cases (n=60)	$\chi 2$ value	P value
Age				
Early adulthood (19-30 years)	33	37	0.735	0.391^{ns}
Adulthood (30-50years; n=53)	30	23		
Gender				
Male (n=93)	51	42	1.449	0.228^{ns}
Female (n=30)	12	18		
Educational status				
Primary (n=28)	10	18	0.296	0.585^{ns}
Secondary (n=42)	19	23		
Graduate (n=53)	34	19		

ns- Not significant (P>0.05)

Table 2. Cognitive score in demographics of the study population

Demographics	Controls (n=63)		Cases (n=60)		P value
	MMSE	MOCA	MMSE	MOCA	
Age					
Early adulthood (19-30 years)	26.93±2.35	24.54±2.58	20.45±3.04	17.86±3.19	$<0.05^{a,b}$
Adulthood (30-50years)	27.00±2.71	24.26±3.32	19.80±2.88	17.30±2.97	$<0.05^{a,b}$
P value	0.9248^{c}	0.7200^{d}	0.4758^{c}	0.5001^{d}	
Gender					
Male	28.00±2.04	26.08±2.10	20.90±2.67	18.40±2.81	$<0.05^{a,b}$
Female	26.72±2.57	23.74±3.18	18.38±3.09	15.88±3.08	$<0.05^{a,b}$
P value	0.1148^{e}	$<0.05^{f}$	$<0.05^{e}$	$<0.05^{f}$	
Educational status					
Primary	26.50±2.17	23.80±3.39	19.77±2.18	17.22±2.29	$<0.05^{a,b}$
Secondary	26.26±2.44	23.00±2.30	20.00±3.84	17.13±3.68	$<0.05^{a,b}$
Graduate	27.50±2.58	24.97±3.29	20.68±2.58	18.68±2.86	$<0.05^{a,b}$
P value	0.7991^{g}	0.4579^{h}	0.8281^{g}	0.9268^{h}	

Significant P values (<0.05) are in bold face
[a]P value of MMSE score (mean ± SD) Vs MOCA score (mean ± SD) in controls
[b]P value of MMSE score (mean ± SD) Vs MOCA score (mean ± SD) in cases
[c]P value of MMSE score (mean ± SD) of Early adulthood vs. Adulthood
[d]P value of MOCA score (mean ± SD) of Early adulthood vs. Adulthood
[e]P value of MMSE score (mean ± SD) of Male vs. Female
[f]P value of MOCA score (mean ± SD) of Male vs. Female
[g]P value of MMSE score (mean ± SD) of Primary vs. secondary vs. graduates
[h]P value of MOCA score (mean ± SD) of Primary vs. secondary vs. graduates

Table 3. Comparison between MMSE and MOCA on different cognitive status of controls and cases (n=123)

Variables	Controls (n=63)		Cases (n=60)		P value*
	Number (%)	Cognitive score (mean ± SD)	Number (%)	Cognitive score (mean ± SD)	
MMSE score (0-30)					
Normal (>24)	55 (87.30%)	27.60±1.88	3 (5%)	25.33±0.57	<0.05[a]
Mild cognitive impairment (21-24)	6 (9.52%)	23.66±0.51	25 (41.55%)	22.56±0.96	<0.05[a]
Moderate cognitive impairment (10-20)	2 (3.17%)	19.50±0.70	32 (53.33%)	17.78 ± 1.86	<0.05[a]
Severe cognitive impairment (< 10)	-	-	-	-	-
P value*	-	<0.05[b]	-	<0.05[b]	-
MOCA score (0-30)					
Normal (≥ 26)	19 (30.15%)	28.00±1.10	-	-	-
Mild cognitive impairment (<26)	44 (69.85%)	22.54±2.10	60 (100%)	21.65±1.86	<0.05[a]
P value*	-	<0.05[b]	-	-	-

* [a] P value of cognitive score (mean ± SD) of controls vs. cases (Student 't' test)
* [b] P value of cognitive score (mean ± SD) of normal vs. mild vs. moderate or severe cognitive impairment (One way ANOVA)
Significant P values (<0.05) are in bold face

Table 4. MMSE Vs. MOCA on association between phenytoin concentration and cognitive status in cases (n=60)

Variable	MMSE			MOCA		
	Pearson r	95% confidence interval	P value	Pearson r	95% confidence interval	P value
Serum phenytoin concentration	-0.0201	-0.3243 to 0.1809	0.5606[ns]	-0.0226	-0.3090 to 0.1973	0.6507[ns]

ns- Not significant (P>0.05)