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Research Brief

Is the use of high-intensity atorvastatin associated with memory impairment?☆

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ABSTRACT

High-intensity statins are the cornerstone of medical management in Acute Coronary Syndromes (ACS). However, their effect on neurocognition are less clear. In this prospective observational study, we gave guideline-directed high-intensity atorvastatin 40 mg to middle-aged statin-naïve ACS patients. Memory assessments were performed before and 6 months after statin therapy using 2 validated scales-the Post-Graduate Institute Memory Scale (PGI-MS), and the Logical Memory Passage Test (LMPT). There was no significant difference in the mean PGI-MS test scores (baseline 75.4 ± 7.9, 6months 76.5 ± 8.2;p = 0.26) or the overall composite scores (baseline 32.02 ± 3.2, 6months 32.8 ± 3.1; p = 0.20), after 6 months of statin use. There was a small improvement in immediate recall (baseline score 8.5 ± 2.5, 6 months 9.04 ± 1.8; p = 0.05), and delayed recall (baseline 6.1 ± 2.6, 6 months 6.9 ± 1.9, p = 0.002). High-intensity atorvastatin use did not affect memory at 6 months among statin-naïve middle-aged patients with ACS.

1. Introduction

The cardiovascular benefits of statins and their safety with prolonged use are well established.[1] However, the data for their effect on neurocognition are less clear and contradicting. Neurocognition has 4 domains - executive function, memory, language, and visuospatial ability.[2] Cognitive impairment is defined as a decline from baseline in any of the 4 domains. Statins are widely prescribed drugs therefore, even a low incidence of memory impairment would be of great clinical significance. Previous studies on statins had shown mixed results with a few studies showing memory impairment, and others showing a paradoxical improvement in memory with its use.[3] To further explore this question, we performed a prospective observational study to assess memory impairment in statin naïve middle-aged ACS patients receiving high dose atorvastatin.

2. Methods

This was a prospective observational study conducted from October 2016 to November 2017. We enrolled statin-naïve adult patients with ACS admitted from the emergency ward in our tertiary care hospital. Patients with baseline memory impairment or risk factors for cognitive dysfunction, such as hypothyroidism, prior Vitamin B12 deficiency, chronic alcohol consumption, stroke, CNS infections, uraemia, liver cirrhosis, psychiatric illnesses, or use of any drugs affecting memory were excluded from the study. All participants received guideline-directed medical therapy.

Memory was assessed using the PGI Memory Scale (PGI-MS) and Logical Memory Passage Test (LMPT) once at baseline and again at the end of 6 months. These consist of a short, simple yet comprehensive battery of tests encompassing ten memory domains. Both tests have been validated in the Indian population. We calculated mean PGI-MS, LMPT scores for immediate recall (IR) and delayed recall (DR), and a composite score based on the

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Table 1
Baseline patient characteristics.

Demographic characteristics Of Participant completing follow-up	($n = 75$)
Male %	72 (96%)
Age (years)	47 ± 8
Patient with Anterior wall myocardial infarction	44 (59%)
Patients with Inferior or Posterior wall myocardial infarction	29 39%)
• Type 2 diabetes mellitus	23 31%)
• Hypertension	24 32%)
• Smoking	47 (63%)
Education Level of Participants	
Less than 5 year of Schooling	14 (19%)
6–9 Year Of schooling	42 (56%)
>10 Year of Schooling	19 (25%)

Data are expressed as means ± SD or counts and percentages, as appropriate.

measurement of 4 particular domains among 10 PGI-MS parameters consisting of recent memory, attention,and concentration, IR and DR.[4] Memory impairment was defined as a difference in any of the test scores of >1 Standard deviation (SD) for age-adjusted normative data. The primary outcome of the study was a difference of more than 1 SD in the PGI-MS test score before and 6 months after atorvastatin therapy.

We enrolled consecutive eligible patients based on a convenience sample during the study period. With the current sample size, this study has over 95% power to exclude 1 SD difference in the PGI-MS test score at an α level of 0.01. Quantitative data were expressed as mean ± SD or median (IQR), as appropriate. The change from pre-to post-statin therapy was assessed by paired *t*-test or Mann–Whitney *U* test as appropriate. A *p*-value less than 0.05 was considered statistically significant. All analyses were performed using STATA14 (StataCorp, College Station, Texas).

3. Results

Of 301 patients admitted with ACS, 85 patients met the inclusion criteria and were included in the study. After applying the exclusion criteria, a follow-up memory assessment at 6 months was performed in 75 patients.

Baseline characteristics are described in Table 1. The mean age of the patients was 47 years (range 28–60 years). About a third of patients had hypertension and diabetes and two-thirds were current smokers. All study participants were given atorvastatin 40 mg during the index admission. The mean follow-up duration for memory assessment was 6 months.

There was no significant change in the scores on the PGI-MS with statin treatment (score at baseline,75.4 ± 7.9, and 76.5 ± 8.2 at follow-up, p = 0.26) or composite score (32.0 ± 3.2 at baseline, and 32.8 ± 3.1 at follow-up p = 0.2). IR and DR function of memory assessed by LMPT showed small improvements (IR baseline 8.5 ± 2.5, 6 months 9.0 ± 1.8; *p*-value = 0.05; DR function, baseline 6.1 ± 2.6, 6months 6.9 ± 1.9, P-value = 0.002) (Table 2).

4. Discussion

This prospective observational study suggests that high-intensity atorvastatin therapy is not associated with any significant change in memory, among middle-aged statin-naïve patients.

One possible explanation for the difference from previous studies may be related to the tools used for memory assessment. Compared to the Mini-Mental Status Examination (MMSE), the PGI-MS and the LMPT assess a wide range of memory domains. They have a good correlation with the Boston Memory Scale (R = 0.71) and the Wechsler Memory Scale(R = 0.85).[5] Another possible explanation may be the various genetic polymorphisms of statin metabolism such as SLCO1B1 gene 388 A > G (Asn130Asp, rs2306283) and 521 T > C (Val174Ala, rs4149056) present in the general population which can alter blood levels of statins.[6] It has been well studied for statin-associated myalgia; the effect on memory impairment is unclear.

In 2012US Food and drugs administration (FDA) issued a report to include cognitive impairment as one of the adverse events of statin consumptionbased on case reports showing mild reversible neurocognitive impairment in 60 patients.[7] The statin users in these reports were older, with a high prevalence of age-related cognitive decline. Previous studies were also limited by their retrospective design, heterogeneous patient populations, type of statin and dosage,and definition of memory impairment.[8,9] In this study, we addressed some of these limitations by recruiting a relatively homogenous population, with no baseline memory impairment, and used fixed-dose of atorvastatin.

Our results are consistent with the evidence from the available randomized control trials (RCT) such as the Pravastatin in elderly individuals at risk of vascular disease (PROSPER), and the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm –(ASCOT-LLA), which found no significant effect of statins on cognition.[10,11] A meta-analysis of 23 RCTs to assess the adverse effects of statins on cognition also showed no difference between the statin and no statin groups for global attention, executive memory, processing speed, and working memory domains (standardized mean difference SMD = 0.01; 95% CI −0.01 to 0.03).[12]

Our study has several limitations. The population included relatively young patients who are at low risk of having memory impairment. This outcome cannot be generalized to the usage of other statins. Inadvertent administration of anxiolytics and sedatives in certain cases either pre-arrival or during emergency management of MI may have affected pre-test parameters, although we carefully screened for such instances. No special efforts were taken to measure statin compliance in our patients. The follow-up period

Table 2
Memory Assessment at baseline and follow up.

PARAMETERS	Baseline	6 months Follow-up
Mean PGI Memory Score	75.4 ± 7.9	76.6 ± 8.4
Patients with PGI MS SD Score < -1	9 (12%)	7 (9.3%)
Composite Score (Recent Memory, Attention, Immediate recall & delayed recall)	32.0 ± 3.2	32.8 ± 3.1
Mean Logical Memory Passage IR[a]	8.5 ± 2.5	9.0 ± 1.8
Mean Logical Memory Passage DR[a]	6.1 ± 2.6	6.9 ± 1.9
Patients with Logical Memory Passage IR Below 15th **percentile**	6 (8%)	4 (5%)
Patients with Logical Memory Passage DR Below 15th **percentile**	28 (37%)	21 (28%)

Data are expressed as means ± SD or counts and percentages, as appropriate.
Abbreviations: PGI-MS – Post graduate institute of medical sciences–memory scale, IR – immediate recall, DR-delayed recall, SD – Standard deviation.
[a] These values represent the actual patient score of Logical memory passage, Percentile scores were also similar.

was short. The effects on memory after long-term high-intensity statin administration needs to be further studied.

5. Conclusion

High-intensity statin atorvastatin (40 mg) use in the treatment of ACS in middle-aged statin-naïve patients is not associated with memory impairment. These data may be reassuring to patients using high-intensity atorvastatin.

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Declaration of competing interest

The authors have no disclosures.

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