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Original Research Article

Effect of combination of glucocorticoid and different doses of atorvastatin on neural function, blood lipid levels and magnetic resonance imaging in patients with multiple sclerosis

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Abstract

Purpose: *To determine the efficacy of the combination of glucocorticoid and different doses of atorvastatin in the treatment of patients with multiple sclerosis (MS).*
Methods: *Sixty MS patients treated at Heping Hospital Affiliated to Changzhi Medical College from January 2020 to June 2021, were equally and randomly assigned to study group (OG) and control group (CG). Patients in OG were treated with glucocorticoid and atorvastatin (half in low-dose, LDG; 20 mg/day) and the other half, in high-dose atorvastatin (HDG, 40 mg/day)). Patients in CG were treated with glucocorticoid and placebo. Changes in magnetic resonance imaging (MRI), blood lipids, RhoA, and neural function were determined.*
Results: *After treatment, Expanded Disability Status Scale (EDSS) score was lower in HDG than in LDG and CG ($p < 0.05$). Total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and lipoprotein a (LP(a)) were significantly reduced and followed the rank order: HDG < LDG < CG ($p < 0.05$). No appreciable differences occurred in HDL-C levels amongst HDG, LDG and CG ($p > 0.05$). Furthermore, RhoA levels were lower in HDG than in LDG and CG, with lower levels in LDG than in CG ($p < 0.05$). There were lower numbers of T2 lesions in HDG than in LDG and CG at 28 days, 3, 6 and 12 months, post-treatment ($p < 0.05$).*
Conclusion: *Glucocorticoid and high-dose atorvastatin combination is better at reducing neurological dysfunction and improving blood lipid indicators in MS patients. This finding may provide a useful guide in the determination of the optimal dose of atorvastatin.*

Keywords: *Atorvastatin, Glucocorticoid, Multiple sclerosis (MS), MRI performance*

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INTRODUCTION

Multiple sclerosis (MS) is a rare autoimmune disease characterized by demyelinating lesions in the white matter of the central nervous system (CNS) [1]. At present, the pathogenesis of MS has not been elucidated [2]. Recent studies showed that serum lipids are closely associated with the occurrence and development of MS. Triglycerides (TGs) and cholesterol are major components of blood lipids [3]. Lipoproteins participate in the regulation of the CNS through

mechanisms related to systemic lipid metabolism, and they exert significant impact on normal neurological function [4]. Studies have revealed that TG levels are generally higher in patients with secondary-progressive MS (SPMS) than in remission (MES) and relapse (REL) patients [5]. This finding indicates that the mechanism of neuropathy is closely related to abnormal lipid levels, and that high lipid concentrations may enhance the progression of MS. It has been reported that high TG levels are independently associated with poor Expanded Disability Status Scale (EDSS) scores, suggesting that high lipid concentrations negatively affect the prognosis of MS in patients [6].

Statins are currently used clinically as lipid-lowering agents in the treatment of cardiovascular and cerebrovascular diseases. Statins inhibit HMG-CoA reductase which is necessary for the production of L-mevalonic acid, thereby lowering blood cholesterol levels [7]. With respect to MS treatment, related studies on statins have been focused mainly on immunomodulation. Thus, there are no studies aimed at investigating whether the lipid-lowering effect of statins may improve therapeutic outcomes in MS patients. In addition to statins, glucocorticoids are frequently used to treat MS. However, there are limited studies on the combined use of atorvastatin and glucocorticoids for MS therapy. The few studies which were done in and outside China, involved small numbers of cases, and the mechanism underlying the combined therapy was not elucidated.

Based on this, the present study was carried out to investigate the effect of combination of atorvastatin and glucocorticoid on MS patients.

METHODS

Patient profiles

Sixty MS patients treated at *Heping Hospital Affiliated to Changzhi Medical College* from January 2020 to June 2021, were selected as the study subjects. The patients were diagnosed with MS via nerve localization signs, MRI examination, and routine biochemical indices of cerebrospinal fluid, in line with the McDonald diagnosis criteria for MS [8]. Each patient had a stable remitting stage which lasted for over 6 months before the onset. The study received approval from the ethics committee of *Heping Hospital Affiliated to Changzhi Medical College* (approval no, 20191126), and it was carried out in line with the principles in the *World Medical Association Declaration of Helsinki* [9]. The purpose and procedures of the study were explained to the patients and their family members, and they submitted signed informed consent.

Patients with the following conditions were excluded: those who had uncontrolled and severe hypertension, heart failure, diabetes, and other diseases, and patients with disorders in vision, hearing and cognition, as well as mental disorders, severe depression and anxiety. Other patients who were excluded were those who received corticosteroid treatment after onset, or treatments with glucocorticoids, immunosuppressants, or lipid-adjusting agents within 2 months before the study, and those who were allergic to statins.

Grouping of subjects

This was a randomized, single-blind, controlled study. Sixty patients were randomly and equally divided into study group (OG) and control group (CG), with 30 subjects in each group. The OG group was further sub-divided into low-dose atorvastatin group (LDG; 20 mg/day) and high-dose atorvastatin group (HDG; 40 mg/day), with 15 patients in each group. There were no statistically significant differences in general data among LDG, HDG and CG ($p > 0.05$). With respect to gender, the compositions were 7 males and 8 females, 6 males and 9 females, and 14 males and 16 females, respectively, while mean age values were 36.40 ± 12.44, 37.00 ± 13.66 and 36.83 ± 10.79 years, respectively. The values for mean course of disease were 56.20 ± 9.79, 56.27 ± 9.46, and 56.07 ± 10.11 months, while values for frequency of onset were 5.33 ± 1.30, 5.27 ± 1.48 and 5.30 ± 1.35, respectively.

With respect to lesion location, the numbers of cases in LDG with onset at cerebral hemisphere, brain stem, cerebellum, spinal cord, and lesions due to abnormally evoked potential were 8, 4, 2, 4, and 13, respectively, while the corresponding numbers in HDG were 9, 4, 3, 4, 12, respectively. In CG, the numbers were 16, 4, 8, 7, and 27, respectively.

Treatments

Patients in CG received pulse therapy and high dose of glucocorticoid. The initial dose of methylprednisolone (Zhejiang Xianju Pharmaceutical Co. Ltd.; NMPA approval no. H33021520) was 1,000 mg/day. The drug was dissolved in 250 mL of physiological saline and administered via intravenous drip for 3 consecutive days. Thereafter, the dose was

reduced to 500 mg/day, and every 3 days, the dose was reduced by half. When the dose decreased to 60 mg/day, the route of administration was changed from intravenous to oral, with administration of 5 mg tablets (China Sources Zizhu Pharmaceutical Co. Ltd.; NMPA approval no. H11020374). After switching to oral administration, the dose was further reduced to 5 mg per week until completion.

The dose and method of administration of methylprednisolone in OG were the same as in CG. In addition, patients in LDG were orally given 20 mg of atorvastatin calcium tablets (Pfizer Pharmaceutical Co. Ltd.; 20 mg-tablet; NMPA approval no. H20051408) every night for 6 months, while those in HDG were given 40 mg of atorvastatin calcium tablets orally every night for 6 months. In the corresponding period, patients in CG received placebo.

Measurement of parameters

Expanded Disability Status Scale (EDSS)

The Kurtzke EDSS criteria [10] were adopted to assess neural function before and after treatment, and the data were collected before treatment (T_1), and at 7 days (T_2), 14 days (T_3), 21 days (T_4), 28 days (T_5), 3 months (T_6), 6 months (T_7), and 12 months (T_8) after treatment. All patients were individually scored by more than three attending neurologists, and the mean values were used to calculate the scores in the three groups.

Blood lipid levels

At time points T_1 - T_8, fasting venous blood was drawn from each patient for measurement of levels of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), TGs and lipoprotein A (LP(a)), using Sysmex CHEMIX-800 Automatic Biochemical Analyzer (with auxiliary reagents; NMPA (I) 20112403311).

RhoA levels

At time points T_1 - T_8, serum RhoA levels were measured using enzyme-linked immunosorbent assay (ELISA; Beijing Kewei Clinical Diagnostic Reagent Inc.; NMPA approval no. S20060028).

MRI performance

At time points T_1, T_5, T_6, T_7 and T_8, the numbers of T2 lesions in patients were assessed by subjecting them to head MRI (GE Singa Excite 3.0 T MRI; NMPA Registration (I) no. 20153333982).

Statistical analysis

The data processing software used was SPSS 20.0. The results comprised enumeration data and measurement data (expressed as mean ± SD) which were statistically analyzed with χ^2 test and *t*-test, respectively. Differences were considered statistically significant at $p < 0.05$.

RESULTS

EDSS scores

After treatment, the EDSS scores were significantly lower in HDG than in LDG and CG ($p < 0.05$), and were markedly lower in LDG than in CG (Table 1, $p < 0.05$).

Table 1: EDSS scores at various time point

Time point	HDG	LDG	CG
T_1	6.92±0.38*,**	6.87±0.44**	6.85±0.33
T_3	5.23±0.94*,**	5.96±0.80**	6.73±0.31
T_3	4.13±0.76*,**	5.12±0.83**	6.34±0.54
T_4	3.57±0.88*,**	4.36±0.91**	5.46±1.07
T_5	3.49±0.91*,**	4.28±0.97**	4.97±1.02
T_6	3.20±0.87*,**	4.11±0.74**	4.81±0.92
T_7	2.58±0.81*,**	3.86±0.53**	4.61±0.89
T_8	1.97±0.49*,**	2.97±0.67**	3.43±0.71

*$P < 0.05$, versus LDG; ** $p < 0.05$, versus CG

Blood lipid levels

After treatment, levels of TC, LDL-C, TGs and LP(a) were significantly lower in HDG than in LDG and CG, but were significantly lower in LDG than in CG ($p < 0.05$). There were no marked differences in HDL-C levels among the three groups ($p > 0.05$). After treatment, the TC in HDG was decreased to a level below 3.00 mmol/L, while TC levels in LDG and CG were above 3.00 mmol/L, indicating large differences among the three groups. These results are shown in Table 2.

RhoA levels

After treatment, there were significantly lower levels of RhoA in HDG than in LDG and CG ($p < 0.05$). However, there were markedly lower RhoA levels in LDG than in CG ($p < 0.05$). The differences in RhoA between HDG and LDG, and between LDG and CG were close to 3 ng/mL, indicating that the reductions in RhoA level were related to atorvastatin dose (Table 3).

Table 2: Blood lipid levels

Time point	HDG	LDG	CG
TC levels (mmol/L)			
T_1	5.88±0.54*,**	5.89±0.51**	5.85±0.49
T_3	4.23±0.35*,**	4.89±0.24**	5.65±0.33
T_3	3.89±0.24*,**	4.41±0.23**	5.10±0.33
T_4	3.56±0.21*,**	4.22±0.23**	4.86±0.30
T_5	3.23±0.23*,**	3.76±0.23**	4.11±0.35
T_6	3.11±0.23*,**	3.55±0.20**	3.89±0.24
T_7	3.00±0.20*,**	3.46±0.20**	3.74±0.23
T_8	2.68±0.23*,**	3.10±0.13**	3.66±0.25
HDL-C levels (mmol/L)			
T_1	1.23±0.11	1.25±0.12	1.20±0.10
T_3	1.12±0.11	1.15±0.12	1.18±0.11
T_3	1.12±0.05	1.14±0.08	1.16±0.10
T_4	1.10±0.05	1.11±0.06	1.15±0.05
T_5	1.10±0.05	1.11±0.04	1.14±0.08
T_6	1.08±0.05	1.10±0.05	1.11±0.06
T_7	1.05±0.05	1.05±0.06	1.08±0.05
T_8	1.02±0.06	1.03±0.05	1.05±0.04
LDL-C levels (mmol/L)			
T_1	3.48±0.23*,**	3.50±0.22**	3.51±0.24
T_3	3.05±0.21*,**	3.22±0.26**	3.40±0.28
T_3	2.88±0.23*,**	3.10±0.25**	3.28±0.20
T_4	2.64±0.20*,**	2.98±0.20**	3.19±0.22
T_5	2.44±0.21*,**	2.74±0.23**	3.14±0.21
T_6	2.38±0.23*,**	2.68±0.20**	3.10±0.21
T_7	2.28±0.15*,**	2.55±0.23**	2.98±0.23
T_8	2.20±0.18*,**	2.49±0.23**	2.96±0.20
TG levels (mmol/L)			
T_1	2.80±0.23*,**	2.81±0.22**	2.83±0.20
T_3	2.44±0.22*,**	2.68±0.23**	2.82±0.20
T_3	2.35±0.19*,**	2.50±0.20**	2.69±0.23
T_4	2.15±0.15*,**	2.36±0.20**	2.40±0.19
T_5	1.98±0.12*,**	2.25±0.23**	2.38±0.16
T_6	1.64±0.15*,**	1.98±0.22**	2.18±0.15
T_7	1.54±0.12*,**	1.77±0.23**	2.05±0.18
T_8	1.42±0.13*,**	1.68±0.18**	1.97±0.16
LP(a) levels (mg/L)			
T_1	541.65±8.12*,**	542.12±8.50**	541.98±8.23
T_3	456.98±8.50*,**	488.65±8.11**	510.98±8.14
T_3	388.66±8.40*,**	412.65±8.39**	445.65±8.10
T_4	312.65±8.10*,**	365.98±8.21**	398.65±8.55
T_5	275.61±8.22*,**	311.65±8.51**	350.65±8.10
T_6	201.60±8.65*,**	265.90±8.21**	297.22±8.47
T_7	166.20±8.64*,**	178.70±8.10**	199.65±8.23
T_8	124.65±8.56*,**	156.98±8.22**	180.98±8.24

*P < 0.05, versus LDG; **p < 0.05, versus CG

MRI performance

Prior to treatment, the numbers of T2 lesions found in MRI scan were comparable among HDG, LDG and CG (p > 0.05). However, at T_5, T_6, T_7 and T_8, the number of T2 lesions was markedly lower in HDG than in LDG and CG (p < 0.05). The numbers of lesions in LDG and CG were comparable, but significant differences in number of T2 lesions were between HDG and LDG (or CG), demonstrating that atorvastatin significantly and dose-dependently increased treatment outcome (Table 3).

Table 3: RhoA levels (ng/mL) and MRI performance

Time point	HDG	LDG	CG
T_1	22.65±2.15*,**	22.70±2.15**	22.68±2.23
T_3	18.11±2.10*,**	20.65±2.12**	22.48±2.10
T_3	16.24±2.01*,**	19.63±2.11**	21.14±1.98
T_4	14.62±1.65*,**	17.65±1.68**	20.10±1.54
T_5	13.55±1.54*,**	16.22±1.47**	19.10±1.46
T_6	12.10±1.20*,**	15.22±1.33**	18.12±1.20
T_7	10.94±1.02*,**	13.98±1.20**	16.73±1.25
T_8	8.65±0.99*,**	11.32±1.01**	14.82±1.42
MRI performance			
T_1	11.47±2.12	11.40±1.93	11.47±1.84
T_5	9.80±1.72*,**	11.13±1.78	11.43±1.80
T_6	9.13±1.89*,**	10.40±1.67	10.63±1.68
T_7	7.33±1.81*,**	8.93±1.53	9.50±2.05
T_8	6.80±1.64*,**	8.27±1.95	8.40±1.99

*P < 0.05, versus LDG; **p < 0.05, versus CG

DISCUSSION

Multiple sclerosis (MS) is an autoimmune disease characterized clinically by inflammatory cell accumulation, infiltration, and blood-brain barrier disruption. The main pathological change is the formation of multiple demyelinating plaques within the CNS white matter. Cholesterol in blood lipids is an essential factor in the CNS, being closely related to the formation of myelin sheath [11]. The blood-brain barrier is in a compromised state in patients during the acute active phase of MS; peripherally-synthesized cholesterol is carried by lipophorins into the CNS, thereby altering the steady state of cholesterol behind the barrier [12]. It has been reported that chronic hypercholesterolemia aggravated arrhythmic immune response, thereby triggering the extravasation of immune cells such as leukocytes and vascular endothelial cells [13].

Extravasation in brain-activated vascular endothelium is a key element in the pathogenesis of MS. Therefore, hyperlipidemia may work together with many factors in the pathogenesis of MS. In a randomized, double-blind controlled study, results of MRI scan showed that patients who received simvastatin had reduced annual mean degree of atrophy [14]. This indicated that low blood lipid levels are beneficial for the maintenance of brain volume in MS patients. Although the study focused only on the effect of lipid therapy on brain volume in MS patients, it clearly suggests that lowering lipid levels may be a new target for MS treatment.

Statins are inhibitors of 3-hydroxy 3-methylglutaryl-coenzyme A (HMG-CoA) reductase. The statins exert lipid-lowering effects by suppressing the production of L-mevalonic acid [15]. Isoprenoid intermediate products in the mevalonate pathway are membrane lipid

attachment points (receptors) for a variety of intracellular signaling molecules, including GTP-binding proteins such as Ras, Rac, and Rho. Indeed, RhoA is closely involved in maintenance of Th1/Th2 balance, CNS axonal degeneration, and growth inhibition. Down-regulation of RhoA protein expression may enhance the repair of CNS injury [16]. In the present study, RhoA levels were markedly lower in OG which was treated with atorvastatin, indicating the immunomodulatory and anti-inflammatory effects of statins. Atorvastatin dose-dependently regulated lipid levels, thereby affecting treatment outcomes in patients.

Regulation of blood lipids by different doses of atorvastatin is a common strategy in the treatment of cardiovascular and cerebrovascular diseases [17]. A study found that atorvastatin at a dose of 20 mg/day was the best dose for effective lowering of blood lipids in patients with acute cerebral infarction [18]. However, in another study, it was found that 40 mg/day was the optimal loading dose of atorvastatin for patients with acute coronary syndrome [19]. Thus, the lipid-lowering effect of atorvastatin is dose-dependent.

The results of the present study showed that TC, LDL-C, TG, and LP(a) levels after treatment were lower in HDG than in LDG and CG, suggesting a dose-dependent effect of atorvastatin in the treatment of MS. In addition, the EDSS scores and MRI performance were better in HDG than in LDG and CG, which also supports the dose-dependent effect of atorvastatin.

Limitations of the study

The atorvastatin doses of 20 mg/day and 40 mg/day selected for treating MS patients in this study were based on clinical experience and extant literature. Although the results showed that the therapeutic effect of the higher dose (40 mg/day) was better than that of 20 mg/day, the possibility of achieving similar effects with atorvastatin doses lower than 40 mg/day and higher than 20 mg/day remains unclear. Thus, this study did not establish an optimal dose for atorvastatin. This should be investigated in future studies.

CONCLUSION

Atorvastatin at a dose of 40 mg/day, in combination with glucocorticoid, is better than combined use of 20 mg/day of atorvastatin with glucocorticoid in reducing neurological dysfunction and improving blood lipid indicators in MS patients. This finding provides a useful reference for determining the optimal dose of atorvastatin in subsequent studies.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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