ORIGINAL ARTICLE

Intercellular adhesive molecule 1(ICAM-1) and acute ischaemic stroke: Role of statins

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Abstract

Objectives: To demonstrate the differential effect of atorvastatin and rosuvastatin on the Intercellular adhesive molecule 1(ICAM-1) in acute ischaemic stroke (AIS) patients.

Methods: The case-control study was done in the Department of Clinical Pharmacology and Therapeutic, Mustansiriyah University, Baghdad, from May to July, 2020 and involved sixty-six patients with AIS compared with twenty-two healthy controls. They were divided into four groups; Group I: Patients with AIS on atorvastatin therapy (n=22). Group II: Patients with AIS on rosuvastatin therapy (n=22), Group III: Patients with AIS not on statin therapy (n=22), Group IV: Healthy controls (n=22). Anthropometric, lipid, and pressure profiles were evaluated. As well, ICAM-1 serum level was estimated in different treatment groups. SPSS version 20.00 was used for data analysis.

Results ICAM-1 levels were increased in patients with AIS compared to the controls. ICAM-1 serum levels were higher in patients with AIS not on statins therapy compared to the controls (P=0.0001), and it was lower in patients with AIS on statins therapy (77.41±16.46) as compared with patients with AIS not on statin therapy (118.71±10.38), (P=0.001). Besides, there was differential effect of statin therapy on the ICAM-1 serum level, which was higher in patients with AIS on rosuvastatin (72.93±9.03) as compared with patients with AIS on atorvastatin (70.61±10.94), (P=0.44). Stroke risk score (SRS) was lower in patients with AIS on atorvastatin therapy (7.60±2.05) as compared with patients with AIS on rosuvastatin therapy (9.11±2.72), (P=0.04).

Conclusion: ICAM-1 is regarded as a surrogate biomarker of AIS in patients with underlying poor cardio-metabolic profile. Both atorvastatin and rosuvastatin are effective in attenuation of AIS measured by lowering of ICAM-1 serum levels.

Keywords: Acute ischemic stroke, Atorvastatin, Rosuvastatin, Intercellular adhesive molecule 1.
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Introduction

Acute ischaemic stroke (AIS) is a prompt inception of focal neurological deficit for more than 24 hours. AIS represent 70-80% of total stroke caused by different cardio-metabolic risk factors including; hypertension, dyslipidaemia, coagulation disorders, vasculitis and atrial fibrillation.[2]

Different studies identified that hypo-perfused and electrically nonfunctional part of the brain termed ischaemic penumbra in AIS is converted to irreversibly injured tissue over time (known as ischaemic core), but at a rate differs considerably between individuals.[3] However, with a fast reperfusion, this penumbral region can be salvaged and can recover completely. This landmark finding formed the rational for the reperfusion therapies that have transformed outcomes for patients with ischaemic stroke since the first positive trial of stroke thrombolysis.[4]

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Although different mechanisms are involved in AIS pathogenesis, increasing evidence shows that ischaemic injury and inflammation are the central mechanisms in the pathogenesis and progression of AIS. AIS triggers ischaemic cascades, which ultimately results in vascular injury, damage of blood brain barrier (BBB), brain oedema, and permanent cerebral injury.[5]

It has been reported that different biomarkers such as brain natriuretic peptide may reflect underlying cardio-metabolic derangements in patients with AIS.[6]

Intercellular adhesive molecule 1(ICAM-1), also recognized as cluster of differentiation 54 (CD54), is a trans-membrane glycoprotein belonging to immunoglobulin super-family of adhesive molecules, which is important in cell-cell interactions of immunological response.[7] ICAM-1 over-expression is linked with different disorders including; chronic metabolic diseases, inflammatory illnesses, and malignancies. ICAM-1 triggers BBB disruption during AIS via the recruitment of leukocytes toward CNS.[8]

Statins inhibit de novo cholesterol biosynthesis through inhibiting the activity of hydroxyl-methyl-glutaryl-

coenzyme-A (HMG-Co-A) reductase, a rate limiting enzyme in cholesterol biosynthesis.[9] The interruption of mevalonate pathway by statins is with the pleiotropic effects of statins. In addition, administration of statins during AIS may avert stroke sequence and relapse.[10]

Therefore, the aim of the current study was to demonstrate the differential effect of atorvastatin and rosuvastatin on ICAM-1 in patients with AIS

Patients and Methods

This case-control study was completed in the Department of Clinical Pharmacology and therapeutic, College of Medicine, AL-Mustansiriyah University, in collaboration with the Al-Yarmouk Teaching Hospital, Baghdad-Iraq from May to July, 2020. This study was permitted by Scientific Committee and Institutional Review Board, College of Medicine, AL-Mustansiriyah University.

A total of 88 participants (66 patients with AIS and 22 healthy controls) were involved in this study. The sample size was calculated according to the population size regarding 95% confidence interval and 5% marginal error.

The selected 66 patients and healthy controls were divided into the following groups;

Group I: Patients with AIS on atorvastatin therapy (n=22).
Group II: Patients with AIS on rosuvastatin therapy (n=22),
Group III: Patients with AIS not on statin therapy (n=22),
Group IV: Healthy controls (n=22).

Informed verbal consent was obtained from all recruited patients and healthy controls before starting of the study.

Inclusion criteria: Patients age $\geq$ 45 years, with neurological symptoms of AIS within 48 hours and positive findings confirmed by computed tomography (CT) scan and magnetic resonance imaging (MRI).

Exclusion criteria: All patients with renal failure, heart failure, liver failure, thyroid disease, malignancy, head trauma, cerebral haemorrhage, pregnancy and lactation, psychiatric and mental disorders were excluded.

Anthropometric profiles: Body mass index (BMI) was calculated by explicit equation; BMI= BW (kg) /Ht (m^2). Blood pressure profile, including; systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by automated digital sphygmomanometer. Besides, mean arterial pressure (MAP) and pulse pressure (PP) were estimated by specific equations.[11]

Biochemical variables: Five milliliters of blood samples were obtained from patients and healthy controls after an overnight fasting (8-12 hours). The blood samples were centrifuged at 3000/ rpm and kept at (-20 C°) for later analysis. Lipid profile including; triglyceride (TG), total cholesterol (TC), and high-density lipoprotein (HDL), were measured by ELISA kit methods (Abbott, A.S.A) in ARCHITECT C 4000). Though, low density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were measured by specific equations; LDL=TC-HDL-(TG/5), VLDL= TGs/5. Furthermore, Atherogenic Index (AI) =log (TG/HDL), cardiovascular risk index (CVRI) = TG/HDL and cardiac risk ratio (CRR) =TC/HDL were also assessed.[12]

ICAM-1 serum level was measured by utilizing an ELISA kit (MyoBio source, U.S.A.) on the basis of sandwich method.

Evaluation of stroke risk score: Stroke risk score (SRS) was evaluated according to the underlying cardio-metabolic risk factors according to Kate et al. method.[13]

Data of the present study was analyzed by using SPSS version 20 and presented as means and standard deviations. Un-paired student t test was applied to detect the significance of differences between two groups. Besides, one-way analysis of variance (ANOVA) and post-hoc test were applied to detect significance of differences among different treated groups. Level of significance was regarded when P value less than 0.05.

Results

Demographic characteristic: In the present study 66(75%) of contributors were patients with AIS compared to 22(25%) healthy controls with a mean age of 67.81±12.84 years and approximately equal male-female ratio (51.13-48.86%). In addition, 30(45.45%) of patients were cigarette smokers. The duration of AIS was short (days), and most of the patients presented with motor deficits and paralysis 32(48.49%). Besides, AIS patients had different cardio-metabolic disorders including; hypertension, dyslipidaemia, ischaemic heart disease, previous cerebrovascular accidents, and other neurological disorders. Regarding the associated and current pharmacotherapy,44(66.67%) patients were on statins therapy compared with 22(33.37%) patients not on statins therapy (Table-1).

Cardio-metabolic profile in AIS patients: BMI was similar between AIS patients and controls (P=0.34). SBP was greater in AIS patients compared to the controls (P=0.0001), though, it was lower in patients with AIS on statins as compared with the patients with AIS not were on statins therapy (P=0.03). DBP did not significantly differ in patients with AIS compared to the controls (P=0.22). Both PP and MAP were increased in AIS patients compared to the controls (P=0.0001) and (P=0.003) respectively. Further, lipid profiles were higher in AIS

Table-1: Characteristics of the present study.

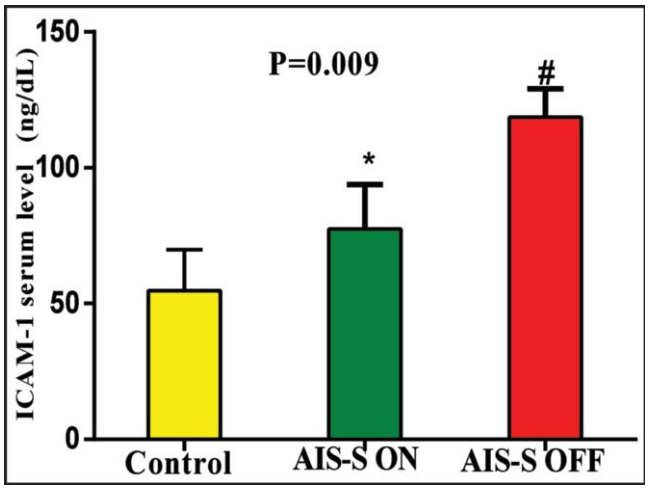
Variables	n, mean ±SD, %
n	88
AIS	66(75.00)
Control	22(25.00)
Age (years)	67.81±12.84
Gender (Male: Female ratio)	45(51.13):43(48.86)
Smoking	30(45.45)
Duration of AIS(days)	1.3±1.03
Clinical Presentation	
Coma	8(12.12)
Paralysis	32(48.49)
Visual loss	7(10.60)
Aphasia and dysphasia	6(9.09)
Convulsion	2(3.03)
Dysphagia	4(6.060
Delirium	7(10.60)
Associated diseases	
Dyslipidaemia	65(98.48)
Hypertension	66(100.00)
IHD	10(27.27)
Previous CVA	22(33.34)
Atrial fibrillation	4(6.06)
Dementia	2(3.03)
Parkinson disease	2(3.03)
Medications	
Statins	44(66.67)
Amlodipine	13(19.69)
ACEIs	8(12.12)
ARBs	14(21.21)
Antiplatelets	32(48.49)
β-blockers	32(48.49)

Data are expressed as N, mean±SD, %, M: F: male: female, IHD: ischemic heart disease, CVAs:cerebro-vascular accidents, ACEIs: angiotensinLconverting enzyme inhibitors, ARBs: angiotensinkreceptor blockers.

patients compared to the control (P=0.0001), while HDL-c was lower in patients with AIS compared to the controls (P=0.0001) (Table-2).

ICAM-1 serum levels: Serum levels of the ICAM-1 were significantly elevated in AIS patients compared to the controls. ICAM-1 serum levels were higher in patients with AIS and not on statins therapy compared to the controls (P=0.0001), alsoICAM-1 serum levels were lower in patients with AIS on statins therapy (77.41±16.46) as compared to patients with AIS not on statins therapy (118.71±10.38), (P=0.001) (Figure-1).

Differential effect of statins therapy on ICAM-1 serum levels of AIS patients: In the current study, there was differential effect of statins therapy on the ICAM-1 serum level which was non-significantly higher in patients with AIS on rosuvastatin (72.93±9.03) as compared with patients with AIS on atorvastatin (70.61±10.94), (P=0.44)

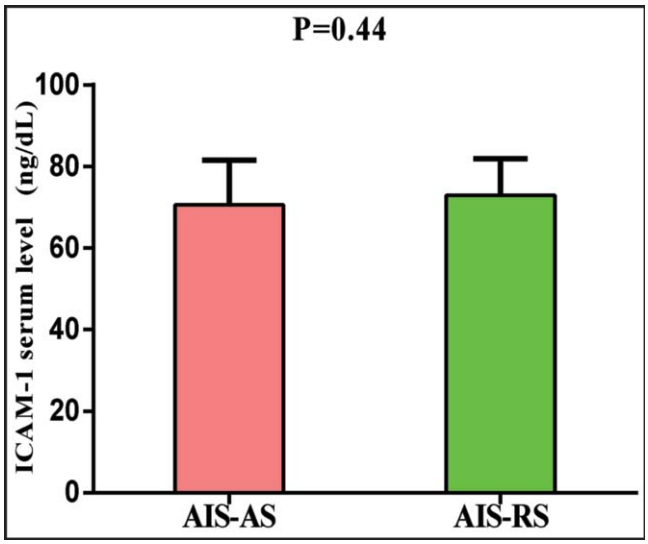


AIS-S ON: AIS patients on statins therapy.
AIS-S OFF: AIS patients not on statins therapy.
*** P <0.05 compared to statins off patients and control.**
 # P<0.01 compared to the control.

Figure-1: ICAM-1 serum level in patients with AIS regarding statins therapy as compared with the controls.

(Figure-2).

Stroke risk score in patients with AIS: Stroke risk score (SRS) was advanced in AIS patients compared with the controls (P<0.0001). SRS was lower (9.10±3.22) in patients with AIS on statins therapy (20.82±7.87) compared with patients with AIS not were on statins therapy (Figure-3). In addition, SRS was lower in patients with AIS on atorvastatin therapy (7.60±2.05) as compared with patients with AIS on rosuvastatin therapy (9.11±2.72),



AIS-RS: AIS patients on rosuvastatin therapy
AIS-AS: AIS patients on atorvastatins therapy.

Figure-2: Differential effect of statins therapy on ICAM-1 in AIS patients.

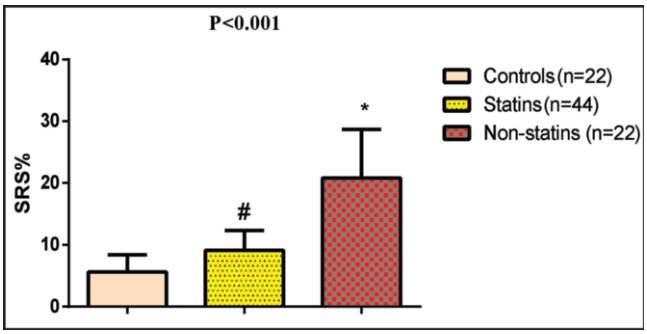
Table-2: Cardio-metabolic profile in patients with acute ischaemic stroke.

Variables	Control (n=22)	AIS(ST) ON (n=44)	AIS(ST) OFF (n=22)	ANOVA
BMI(kg/m^2)	31.87±3.12	31.00±4.47	32.74±5.90	0.34
SBP(mmHg)	130.78±9.07	143.63±12.92#	154.84±15.39*¶	0.0001
DBP(mmHg)	87.32±8.58	89.93±11.51	93.03±11.61	0.22
PP(mmHg)	43.46±6.91	53.70±4.09#	61.81±6.95*¶	0.0001
MAP(mmHg)	101.80±8.73	107.83±9.67#	113.63±11.59¶	0.003
TC(mg/dL)	214.45±30.12	210.66±21.96#	259.95±32.84*	0.0001
TG(mg/dL)	189.80±13.81	193.34±11.71	212.79±14.61*¶	0.0001
HDL-C(mg/dL)	53.79±8.47	48.92±9.06	34.91±5.93*¶	0.0008
non-HDL-C	160.66±21.78	161.74±20.99	225.04±23.81*¶	0.0001
LDL(mg/dL)	122.70±9.63	123.10±8.57	182.50±17.61*¶	0.0001
VLDL(mg/dL)	37.96±8.41	38.66±9.62	42.55±11.56	0.23
LDL/HDL ratio	2.28±1.08	2.51±1.09	5.22±2.05*¶	0.0001
AI	0.18±0.03	0.23±0.03#	0.42±0.06*¶	0.0001
CRR	3.98±1.72	4.30±1.12	7.44±2.81*¶	0.007
CVRI	3.52±1.06	3.95±1.86	6.09±2.84*¶	0.007

Data are presented as mean ±SD, ANOVA test andTukey HSD Post-hoc Test, BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PP: Pulse pressure; MAP: Mean arterial pressure; TC: Total cholesterol; TG: Triglyceride; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; AI: Atherogenic index, CRR: Cardiac Risk Ratio, CVRI: Cardiovascular risk index; ST: Statins.

* P <0.05 compared to statin therapy.

¶# P<0.05 compared to the control.



p<0.001 as compared with statins and control groups.
 # p<0.05 as compared with control group.

Figure-3: Stroke risk score in AIS patients regarding statins therapy.

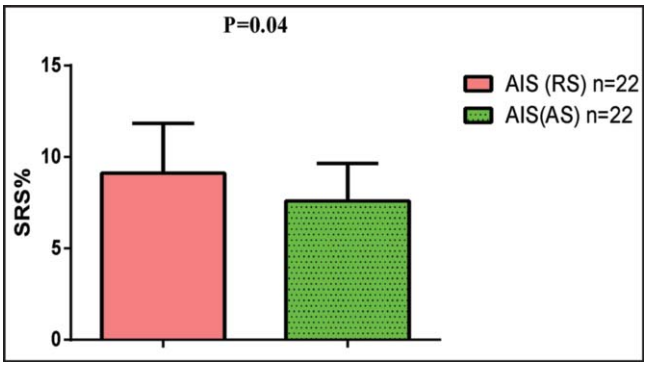


Figure-4: Stroke risk score in AIS patients on atorvastatin or rosuvastatin therapy.

(P=0.04) (Figure-4).

Discussion

AIS is one of the most important causes of mortality and disability in the developing countries. Of note, AIS is a dynamic process of several reactions, such as immunological response, oxidative stress, reactive gliosis, and dysfunction of homeostatic system.[14]

Studies suggest that inflammation has a role in the pathogenesis of AIS. Neuro-inflammation exacerbates the injury by inducing cell death, which also plays an advantageous role in promoting of cells recovery.[15]

ICAM-1 is a cell-bounded glycoprotein that participates in inflammation through interacting with lymphocytes, since it is expressed in astrocytes, endothelial cells, and microglia. As well, ICAM-1 affects BBB integrity and might be a useful biomarker for post-stroke inflammation.[16]

In the present study, ICAM-1 serum level was higher in AIS patients compared with controls. Since there is a noteworthy association between ICAM-1 and AIS, and mounting evidence suggests a possible association between ICAM-1serum level and severity of AIS as it linked with ischaemia-associated BBB injury.[17]

Kurkowska et al., proposed that ICAM-1 may act as an early biomarker for endothelial disruption in the acute phase of AIS.[18]

In the present study, ICAM-1 level was reduced in statins-On AIS patients compared to statins-Off AIS patients. However, there was no significant association between statins and ICAM-1serum levels in patients undergoing percutaneous cardiac intervention.[19]

Kurkowska et al showed a decrement in ICAM-1 serum level following using of statins due to attenuation of ICAM-1-induced endothelial disruption.[20]

Petit et al suggested that statins may inhibit ICAM-1 through preventing ICAM-1 from interacting with lymphocyte function-associated antigen-1 (LFA-1), thus limiting the exacerbation of inflammatory reaction.[21]

In the present study, ICAM-1 was non-significantly reduced in AIS patients on atorvastatin therapy compared to AIS patients on rosuvastatin therapy. Bubnova et al., illustrated an insignificant difference between the effect of atorvastatin or rosuvastatin in ameliorating AIS-associated inflammation and disruption of BBB.[22]

Similarly, rosuvastatin inhibits appearance of adhesion molecules (ICAM-1and VCAM-1) production through inhibition of p38-mitogen activated protein kinase (MAPK) pathway in AIS.[23]

Therefore, both atorvastatin and rosuvastatin improve endothelial inflammatory changes through modulation of inflammatory adhesion molecules in patients with AIS.

However, SRS was more linked with ICAM-1 in AIS patients not on statin therapy. This correlation gives a clue about the association between stroke risk and inflammatory/pro-inflammatory axis. It has been reported that poor cardio-metabolic risk factors are associated with chronic inflammatory reaction, which in turn increase the risk of AIS.[24] On the other hand, statins therapy reduces dyslipidaemia and systemic hypertension, thereby reducing neuronal damage in patients with AIS.[25] Thus, SRS in the present study was less correlated with the studied biomarkers in AIS patients on statins therapy.

The present study had several limitations including; small sample size and pro-inflammatory cytokines like tumour necrosis factor alpha (TNF-α), which affects both cardio-metabolic profile and AIS was not measured. However, the present study provided evidence in association between AIS patients and ICAM-1 serum level. Enormous prospective and clinical trial studies are warranted in this regard to confirm the association between AIS and ICAM-1 serum level.

Conclusion

ICAM-1 is regarded as a surrogate biomarker of AIS in patients with underlying poor cardio-metabolic profile. Both atorvastatin and rosuvastatin are effective in attenuation of AIS measured by lowering of ICAM-1 serum levels.

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Conflict of Interest: None.

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