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Original Article

Internal Medicine Section

The Effect of Statins Use on the Risk and Outcome of Acute Bacterial Infections in Adult Patients

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ABSTRACT

Background: Beyond their lipid-lowering abilities, statins have anti-inflammatory and immunomodulatory properties. In view of these effects, a growing interest has emerged in the possible role of statins, in preventing or decreasing morbidity and mortality from infection.

Objectives: The aim of this study was to determine whether previous statin use is associated with reduced risk of acute bacterial infections and better outcome of these infections.

Materials and Methods: In this historical cohort study, consecutive adult patients admitted with acute bacterial infection were enrolled. Control group were selected from adult outpatient and without history of acute bacterial infections. Acute bacterial infections included in this study were; pneumonia, acute pyelonephritis, cellulitis and sepsis with unknown origin. Data about baseline characteristics, co-morbidities and statins use of two groups was obtained.

Results: Finally 144 patients met inclusion criteria and were enrolled. Same numbers of controls were selected. Two groups were matched based on most baseline characteristics and co-morbidities. The patients' categories were as follows: pneumonia 42.3%, acute pyelonephritis 23.6%, cellulitis 16% and sepsis 18%. From all participants 29.9% of patients and 45.8% controls were statin users. There was significant association between previous statin use and reduced risk of acute bacterial infections (Mantel Haenszel Weighted Odds Ratio=0.51, 95% CI: 0.30-0.85, p=0.009). Duration of hospitalization was significantly shorter in statin users (p=0.002). Hospital mortality rate was lower (14.6%) in statins users when compared with non-users (18.8%) with significant difference (p=0.028).

Conclusion: Prior therapy with statins is associated with considerably reduced onset of acute bacterial infections and better outcome in adult patients.

Keywords: Acute pyelonephritis, Immunomodulatory properties, Sepsis

INTRODUCTION

The developing and introduction of statins as treatment for hyperlipidemia led to significant advance in the prevention of coronary artery disease. Their effects on hypercholesterolemia is mediated by inhibiting 3-Hydroxy-3-methylglutaryl coenzyme A [1].

During recent years, numerous studies have described different effects of statins in addition to their lipid-lowering ability. These effects have been reported to be related to very different metabolic pathways. One of them is the anti-inflammatory and immunomodulatory properties of statins which include the modulation of both innate and adaptive immune system [2]. Such effects could arise from influence on the inflammatory response including decreased production of cytokines. In addition, they modify the intercellular interactions and the cellular chemotaxis of the immune system [3]. On the other hand; statins have been shown to have direct inhibitory effects on some pathogenic microorganisms [4].

In view of these effects, a growing interest has emerged in the possible role of statins in preventing or decreasing morbidity and mortality from infection [5]. In animal models studies, statins use has been associated with some benefit in several infectious diseases [6-8]. Some clinical studies in human have showed that previous treatment with statins was associated with decreased rates and or mortality in patients with community acquired bacterial infections [9-12]. Also, some meta-analyses have shown beneficial roles of statins in the prevention and treatment of several different types of infections [13-15].

Despite this, some study not confirmed these effects. Finding of one systematic review and meta-analysis of randomized placebo controlled trial did not support the hypothesis that statins reduce the risk of infections and authors recommended more relevant studies [16].

Most of these previous studies have been conducted on one specific type of infections. On the other hand most of these studies did not specify which types of statin were prescribed. We designed this study in community dwelling adult people to explore whether patients who receive statins are less likely to develop acute bacterial infections. If the history of statins use was less common in patients with acute bacterial infection, we can conclude that statins use may have protective effects against development of bacterial infections. Also, we evaluated whether pretreatment with statins can affect the outcome in patients with bacterial infections.

MATERIALS AND METHODS

This was a retrospective cohort study conducted from June 2012 to August 2013 at a university-affiliated hospital in Tehran, Iran. Adult patients older than 18 years who were admitted with acute bacterial infections were considered for participation in the study. Adult outpatients who visited the hospital and if had no history of acute bacterial infections, were considered for control group from all participants informed written consent was obtained before enrollment.

Patients with acute pneumonia, acute pyelonephritis, cellulitis and sepsis with unknown origin were included as cases. Baseline data was collected including age, gender, underlying medical conditions, smoking and alcoholism. We included the following underlying medical conditions in our study: diabetes mellitus, ischemic heart diseases, hypertension, chronic obstructive pulmonary diseases, benign prostatic hypertrophia and urinary stone.

All participants were divided into two subgroups on the basis of statins use. Statin user group were defined as patients who received statin at least for three months prior to the inclusion in study. Statins non-users group had no history of statin use. For comparision adult out patients as controls were also divided into user and non-user

of statins. Intermittent statin users were excluded. Statins included in our analysis included simvastatin and atorvastatin that are the most common types of statins used (dose range, 10-40 mg/day). Patients were followed until discharge from hospital or death. The outcome was defined as cure or death. Individuals with history of chronic renal diseases, immunocompromised state, or receiving immunosuppressive drugs were excluded. We defined each type of acute bacterial infections based on clinical, laboratory and radiographic diagnostic criteria that was confirmed by a specialist in infectious diseases. The study protocol was approved by Research Council and Ethical Committee of the Semnan University of Medical Science.

STATISTICAL ANALYSIS

Statistical analysis was performed by Kolmogorov-Smirnov, Chi-Square, Student's t, Mann-Whitney tests and Mantel Haenszel Weighted Odds Ratio using SPSS16.0, EPI 8.0 software's. A p-value less than 0.05 considered statistically significant.

RESULTS

Of all patients admitted with presumed bacterial infection that were screened 144 met inclusion criteria and were enrolled. Same numbers of controls were selected. The mean (± SD) age of patients was 57.9 ±10.2 years and the controls was 53.9 ±11 that showed statistically significant difference (p=0.02). 51.4% of cases and 54.2% of controls were male with no significant difference (p=0.637). Baseline characteristics and co-morbidities of two groups are showed in [Table/Fig-1]. Two groups were matched based on these characteristics.

Characteristics	Study group				p-value
	Case (n=144)		Control (n=144)		
	n	%	n	%	
Gender					
Male	74	51.4	78	54.2	
Female	70	48.6	66	45.8	0.637
Smoke					
+	56	38.9	47	32.6	0.269
-	88	61.1	97	67.4	
Alcohol					
+	32	22.2	37	25.7	0.490
-	112	77.8	107	74.3	
Diabetes Mellitus					
+	39	27.1	33	22.9	0.414
-	105	72.9	111	77.1	
COPD*					
+	34	23.6	27	18.8	0.313
-	110	76.4	117	81.2	
Ischemic heart disease					
+	28	19.4	22	15.3	0.351
-	116	80.6	122	84.7	
Hypertension					
+	49	34.0	52	36.1	0.711
-	95	64.0	92	63.9	
BPH†					
+	19	13.2	19	13.2	-
-	125	86.8	125	86.8	
Urinary stone					
+	14	9.7	11	7.6	0.530
-	130	90.3	133	92.4	

[Table/Fig-1]: Baseline characteristics and co-morbidities of two groups
*Chronic obstructive pulmonary diseases, †Benign prostatic hypertrophia

The patients categories on admission to the hospital were as follows: pneumonia 61 (42.3%), acute pyelonephritis 34 (23.6%), cellulitis 23 (16%) and sepsis 26 (18%). Of patients who met study criteria 29.9% were statin user (22.2% atrovastatin and 7.6% simvastatin). In controls 45.8% were statin user (33.3% strovastatin and 12.5% simvastatin). There was significant association between previous statin use and risk of acute bacterial infections (Mantel Haenszel Weighted Odds Ratio=0.51, 95% CI: 0.30-0.85, p=0.009). The mean (± SD) duration of statins use was 325±38.0 and 447±61 days in cases and control respectively with significant difference (p<0.001).

When data analysed based on type of statin (atrovastatin versus simvastatin), this association was significant for atrovastatin (Mantel Haenszel Weighted Odds Ratio=0.53, 95% CI: 0.29-0.92, p=0.025) but not for simvastatin (Mantel Haenszel Weighted Odds Ratio=0.46, 95% CI: 0.19-1.12, p=0.098). When data was analysed based on age group, the relationship was significant for patients above 60-year-old [Table/Fig-2].

The mean (± SD) duration of hospitalization was 9.0± 2.2 days for statin users and 10.6± 3.1 days for non-users. Duration of hospitalization was significantly shorter in statin users (p=0.002). Hospital mortality rate was lower (14.6%) in statin users when compared with non-users (18.8%) with significant difference (p=0.028).

Age (years)	Type of statins	Study group				OR*	95% CI† for OR	p
		case		Control				
		n	%	n	%			
<50	Atorvastatin							
	+	12	35.3	14	34.1	1.05	0.36-3.04	0.918
	-	22	64.7	27	65.9			
	Simvastatin							
	+	2	8.3	6	18.2	0.41	0.05-2.62	0.295
	-	22	91.7	27	81.8			
	All statin user							
	+	14	38.9	20	46.6	0.86	0.32-2.28	0.738
	-	22	61.1	27	57.4			
50-59	Atorvastatin							
	+	12	21.8	17	37.0	0.48	0.18-1.24	0.096
	-	43	78.2	29	63.0			
	Simvastatin							
	+	6	12.2	6	17.1	0.67	0.17-2.67	0.530
	-	43	87.8	29	82.9			
	All statin user							
	+	18	29.5	23	44.4	0.530	0.230-1.23	0.106
	-	43	70.5	29	55.8			
≥60	Atorvastatin							
	+	8	18.2	17	43.6	0.29	0.09-0.86	0.012
	-	36	81.8	22	56.4			
	Simvastatin							
	+	3	7.7	6	21.4	0.31	0.05-1.59	0.107
	-	36	92.3	22	78.6			
	All statin user							
	+	11	23.4	23	51.1	0.29	0.11-0.78	0.006
	-	36	76.6	22	48.9			

[Table/Fig-2]: Statins use and risk of acute bacterial infections in different age groups
*OR: Odds Risk †CI: Confidence Interval

DISCUSSION

In this study, it was found that rate of statins use was more common in individuals without acute bacterial infections. Also, duration

of use was longer in controls group. These findings can lead to this hypothesis that previous statins use may be associated with a decreased risk of acute bacterial infections. The fact that no significant difference was observed in most underlying conditions and co-morbidity highlight this finding. These finding confirm previous evidence that statins may have immunomodulatory and anti-inflammatory properties in addition to their lipid lowering effects. In addition, statins also seem to attenuate the replication and infectivity of several infectious pathogens [17,18].

This finding is comparable with most previous studies describing the association between statin use and reduced incidence of infections [10,19-21]. Schlienger et al., did a case-control study within the general practice research database and found an association of statin use with decreased risk of pneumonia (adjusted odds ratio 0.71, 0.56 to 0.89) [22].

The protective effect of statins on rate of infection and outcome was not supported by some studies. For example, a recent meta-analysis of large randomized controlled trials investigated the effects of statins on preventions of infections. The result showed that the use of statins was not associated with decrease in the risk of infection and related adverse events including infection related mortality [16]. In another population-based cohort study conducted on statin users and nonusers in the United Kingdom, the investigators noted that there was no clear evidence for an effect of statins on the risk of infection. They reported a small reduced risk of pneumonia, but the risk of urinary tract infections and other respiratory infections were marginally increased [23]. Some other study reported no effect of statin on reduced risk of pneumonia [24], postoperative wound infections [25,26], and hospital acquired infections [27,28].

On the other hands, some studies reported higher incidence of infections in statin user. Magulick et al., conducted a retrospective cohort study in the San Antonio, USA. Statin users were patients who received a statin for at least 3 months. After adjustments for potential baseline confounders, there were significantly higher odds of having common infection diagnosis among statin users in comparison with nonusers. Common infections included acute respiratory infections, pneumonia, bacteraemia, sepsis, skin infections and urinary tract infections [29]. Fleming and co-workers investigated the effect of current statin use on acute respiratory and urinary tract infections in primary care. Study suggested that there was a benefit of statin use to prevent urinary tract infections, an increased risk for acute bronchitis, and no effects for pneumonia and upper respiratory infections [30]. This difference in these findings might at least partly be explained by differences in the study design, confounding variables, choice of outcome measures, and the different definition of statin user.

One review evaluated the immunomodulatory effects of different types of statin. Statins have direct influences on immune cells and anti-inflammatory intracellular pathways. The authors illustrated that these properties might vary between each statin types [31]. When we compared findings based on two type of statins used in this study, this association was significant for atrovastatin but not for simvastatin. In contrast in a study on diabetic patients the statins effect on considerable reduction in the risk of pneumonia was similar for all statins [19]. Another study assessed the association between current statin use and the risk of community-acquired pneumonia. The study showed a similar association for the two most commonly prescribed statins, atorvastatin and simvastatin [21]. In Daneman et al., study no specific statin showed a significantly decreased risk of surgical site infections [32].

Another finding in our study was the significance difference in mortality between the statin user and non-user groups. This finding suggests that previous statins use may also improve prognosis in patients with bacterial infections. In agreement with this finding the results suggesting an association of statin therapy and decreased mortality in infections are reported with several prior studies [9,33].

In a retrospective study, 388 patients with bacteraemia were evaluated for mortality based on previous statin use. Finding showed significant reduction in both overall and attributable mortality among patients taking statins compared with patients not taking statins. They suggested that statins may have a therapeutic benefit in infections [12]. The physiologic mechanism by which statins may alleviate mortality in sepsis remains undetermined, but may related to the anti-inflammatory and endothelium modulation properties of these medications.

In contrast other studies found no difference in mortality in statin users versus non-users [34-36]. Fernandez et al., conducted a study on 438 ICU patients and reported that patients who were treated with a statin prior to and during their ICU admission had a statistically higher in-hospital mortality than their non-statin counterparts (61% vs. 42%) [27].

Strength of this study was that two group were matched for most underlying conditions and confounding co-morbidities. More specifically, we excluded immunocompromised people, who may be at higher risk of acute bacterial infections.

LIMITATIONS

The study has some limitations. First, the eligible patient number is relatively small in this study, owing to the restrictive inclusion criteria. Second, although two groups were matched for most co-morbidities, it is still possible that some unmeasured co-morbidity may have affected results. Third, the effect of some confounding factors like severity of infection, duration of infection, was not neutralizing in cases subgroups. Another concern is that people on statins take more good health support which can induce confounding effect. More studies especially prospective randomized and with large sample are required to better defining the relationship between statin use and the risk and outcome of infection. Also, determining of optimal effective dose and duration of statin therapy should be undertaken.

CONCLUSION

In this study, we found that patients with acute bacterial infections have lower rate and duration of previous therapy with statins when compared with subjects without infections.

It can be proposed that statins use protect against acute bacterial infections. Satin use also, leads to better outcome in adult patients especially over 60 years old. These effects may be via influence of statins on the inflammatory responses, modifing the intercellular interactions and the cellular chemotaxis of the immune system. Atrovastatin showed better effects. These findings have possible implications that patients with major infections who are already taking statins might be discouraged to stop taking statins. In addition, statins might be considered for patients at very high risk for infections.

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