

Effect of simvastatin on early sepsis in critically ill patients

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Abstract: Sepsis is a leading cause of death in non-coronary ICU patients worldwide. Despite the early goal-directed therapy, low-dose corticosteroids, early antibiotics use and supportive care have been shown to improve survival in patients with severe sepsis, but the number of sepsis related deaths appears to be increasing. Statins or (HMG-CoA) reductase inhibitors, are a class of drug that revolutionised the treatment of hypercholesterolemia. New researches show that statins have a variety of properties that are independent of their lipid lowering ability, which collectively referred to as pleiotropic effects. A recent growing body of evidence suggests that statins may indeed have a protective effect against severe sepsis and reduce the rate of infection-related mortality. This novel primary prevention concept may have far reaching implications for the future management of serious infections. The aim of the present study is to evaluate the effect of statin administration during sepsis in decreasing the incidence of severe sepsis and septic shock and the subsequent development of organ failure and mortality in critically ill patients. This prospective study was performed on 40 adult patients of both sex selected from those admitted to ICU presented with early sepsis. The selected patients were randomized into two groups; the statin group who received 40 mg simvastatin for 10 days in addition to the ordinary conventional therapy of sepsis. And the control group who received the conventional therapy of sepsis only. All the 40 studied patients in both groups were initially assessed on admission at first day of the study. And the effect of statin administration on the progression of sepsis and its outcome was evaluated and monitored daily by laboratory investigations including; WBC, Hco3, CRP, PCT. and clinical assessment and scoring systems (GCS, SOFA). Statins had been found to enhance survival of sepsis by about 25% and decreased incidence of deterioration of early sepsis to severe sepsis and septic shock by about 10% in the statin group. Statins also decreased mortality rate by about 15% in comparison to the non statin group. From the statistical view, the results showed non significant differences between two groups. Statins can be used as a good adjuvant therapy of sepsis in addition to their lipid lowering properties. The statins are more beneficial when used primary in the early phase of sepsis. Statins decrease the worse deterioration of sepsis and the mortality rate but without significant values. This potential role of statins in the treatment of sepsis should be further evaluated in large prospective randomized controlled studies. Future studies are needed for testing the usefulness of combinations of statins with antibiotics against acute sepsis.

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1. Introduction

Sepsis is a leading cause of death in non-coronary ICU patients worldwide. Sepsis has been referred to as a process of malignant autodestructive intravascular inflammatory process. because it is uncontrolled, unregulated exaggerations of the normal pathophysiologic inflammatory response to infection with subsequent loss of the equilibrium between the proinflammatory and anti-inflammatory elements to involve otherwise normal tissue. This can result in the multiple organ dysfunction syndrome (MODS), which represent the more severe end of the spectrum of severity of sepsis.(1,2)

Despite the longstanding therapeutic principles of the early goal-directed therapy, low-dose corticosteroids, early antibiotics use and supportive care have been shown to improve survival in patients with severe sepsis, sepsis remains a

catastrophic enigma because its related mortality remains unacceptably high.(3,4)

Statins are a class of drug that have revolutionised the treatment of hypercholesterolemia. They are the most efficient agents for reducing plasma cholesterol and secondary pathologies such as ischaemic heart disease. They scientifically referred to 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors. (5)

Important progress has been made in recent years showed that statins have a variety of properties independent of their lipid lowering ability. These anti-inflammatory, antioxidant, immunomodulatory, and antiapoptotic antiproliferative, antithrombotic, and endothelium protecting features have been collectively referred to as pleiotropic effects. (6)

A growing body of evidence suggests that statins may indeed have a protective effect against

severe sepsis and reduce the rate of infection-related mortality.(7) This novel primary prevention concept may have far reaching implications for the future improvement of outcome after the onset of sepsis.(8)

Both C-reactive protein (CRP) and procalcitonin (PCT) are a known acceptable sepsis markers. (CRP) is an acute-phase protein that increases rapidly in response to infection, CRP was characterized as a specific marker of infections such as sepsis. It is also useful as prognostic marker as higher CRP levels correlate with a higher risk of organ failure and death, and persistently elevated levels portend a worse prognosis.(9)

PCT is a new highly sensitive and specific marker of bacterial infection, found to be used as a factor of "early infection's phase" in diagnosing sepsis, procalcitonin may serve as an important indicator of the severity and prognosis of infection and allow judgment of the efficacy of therapeutic measures. (10)

2. Patients and Methods

This prospective study was performed on 40 adult patients of both sex, admitted to Critical Medicine department of Alexandria Main University Hospital, who were presented with evidence of infection or early sepsis, PCT > 2 ng/ml and CRP level >50 mg/l. Patients who were presented with severe sepsis or septic shock or had contraindication to statins (e.g. history of liver dysfunction) were excluded.

The selected patients were randomized into two groups; the statin group who received 40 mg simvastatins in addition to the ordinary conventional therapy of sepsis (Early goal- directed therapy, Infection management, Lung protective ventilation). And the control group who received the conventional therapy of sepsis only. The study duration was 10 days, started from the day of admission to ICU.

All the 40 studied patients in both groups were initially assessed on admission at first day of the study as regard; patient data (age & sex), clinical examination and laboratory investigations (routine investigations, complete blood count, renal function tests, bilirubin and serum Na & K).

The effect of statin administration on the progression of sepsis was evaluated and monitored daily by laboratory investigations including; WBC, Hco3-, CRP, PCT. and clinical assessment and scoring by systems (GCS, SOFA). The data obtained was compared with that of the control group.

3. Results

The age in all the 40 patients ranged from 25 to 59 years, 57.5% of the all studied patients were males. There was no significant difference between

both groups as regard the age and sex and in addition to their effect on the outcome of sepsis at the end of the study. Also there was no significant difference between both groups as regard the history of having chronic diseases like (DM-HTN) or pre administration of antibiotics, which may confound the effect of statin on the outcome of sepsis.

In relation to outcome of sepsis, statins lead to non significant decrease in the incidence of deterioration of early sepsis to severe sepsis and septic shock by about 10% in the statin group and non significant decrease in the mortality rate by about 15% in comparison to the non statin group. (Table 1, Figure 1)

In the statin group along the course of the study, the WBC count decreased more than the control group, in opposite to the metabolic acidosis which increased but less than the control group. There were no significant differences between both groups in relation to WBC or metabolic acidosis.

There was significant decrease of the PCT in each group, with no significant differences between both groups. PCT levels were closely correlated with the sepsis and its subsequent developments from deterioration to death (Table 2, Figures 2-3). CRP decreased significantly in each group with significant difference in the statin group from the control group (Figure 4).

Comparing the sensitivity, specificity, positive and negative predictive values and diagnostic accuracies between the PCT and CRP in both groups, our results revealed higher values for PCT levels in all the parameters at the end of study (last reading), these values were more in the statin group. This indicated that PCT was more predictor than CRP (Table 3).

Receiver- operating-characteristic (ROC) curve of PCT of statin group, showed significant increase of the area under the curve of the last day reading than 1st day, revealed higher sensitivity of the last reading of PCT and be a good mortality predictor (Figure 5), but not significant in Group II (Figure 6).

Receiver-operating-characteristic (ROC) curves of CRP levels of statin group showed successive significant increase of the area under the curve along the course of the study, which showing the highest value and sensitivity of CRP at last reading, at this the CRP giving its most accurate percent of mortality prediction. While in control group, the ROC curve showed its highest value at 7th day and return to decrease at the last reading. (Figures 4,5)

The SOFA score was done daily to assess the statin effect on the sepsis and sequential organ dysfunction. Showing that the mean of SOFA score

increased significantly in both groups, but at lower rate in the statin group with no significant difference between both groups (table. 4) In opposite to the GCS which decreased in the statin group with lower rate than control group with significant difference.

In Group I (statin group) and control group there was successive increase of the area under the curve along the course of the study. It showed higher sensitivity of SOFA score at the 7th day and last reading (100%), demonstrating that SOFA score was mainly a good mortality predictor at these readings (Figures 9,10).

4. Discussion

Despite several decades of research and phenomenal advances in technology and therapeutics, sepsis remains a catastrophic enigma. The longstanding therapeutic principles of early antibiotics use and supportive care have been difficult to improve upon. Because so many cascades are

triggered during sepsis, merely blocking a single component may be insufficient to arrest the inflammatory process. (3)

Statins are a class of drug that by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase have revolutionised the treatment of hypercholesterolemia. (5) Statins have a variety of properties that are independent of their lipid lowering ability. These features have been collectively referred to as pleiotropic effects. A growing body of evidence suggests that statins may indeed have a protective effect against severe sepsis and reduce the rate of infection-related mortality. (6)

This prospective study was performed on 40 adult patients, selected from those presented with suspected infection or early sepsis, to evaluate the effect of statin administration during sepsis on decreasing the incidence of severe sepsis and septic shock and the subsequent development of organ failure and mortality in critically ill patients.

Table (1): Comparison between the two studied groups according to prognosis and outcome at the end of the study.

	Statin Group		Control Group		Test of sig.
	No.	%	No.	%	
Improved and discharged	9	45.0	4	20.0	MCp = 0.256
Died	3	15.0	6	30.0	
Sever sepsis & Septic shock	8	40.0	10	50.0	

* : Statistically significant at $p \leq 0.05$; MCp: p for Monte Carlo test

Table (2): Comparison between the two studied groups according to the serum PCT level (ng/ml) at 1st and last day (10th day) of the study.

		1 st day	10 th day	McNemar (p)
Statin Group	<0.5	0	1	20.000* (<0.001)
	>0.5-<2	0	0	
	>2-<10	20	0	
	>10	0	8	
Control Group	<0.5	0	0	19.000* (0.004)
	>0.5-<2	0	1	
	>2-<10	20	0	
	>10	0	10	

Table (3): Sensitivity, specificity, accuracy, positive and negative predictive values of PCT and CRP in both groups.

		PCT		CRP	
		1 st reading	Last reading	1 st reading	Last reading
Statin group	Sensitivity	100.00	90.91	100.00	81.82
	Specificity	0.00	88.89	0.00	88.89
	Accuracy	55.0	90.00	55.00	85.00
	PPV	55.0	90.91	55.00	90.00
	NPV	NA	88.89	NA	80.00
Control group	Sensitivity	100.00	87.50	100.00	81.25
	Specificity	0.00	75.00	0.00	75.00
	Accuracy	80.00	85.00	80.00	80.00
	PPV	80.00	93.33	80.00	92.86
	NPV	NA	60.00	NA	50.00

Table (4): Comparison between the different categories of outcome according to mean SOFA in the studied groups

	Cured and discharge	Septic shock	Died	χ^2 (p)
Statin group				
Range	0.60-4.60	3.20-8.70	5.00-7.40	
Mean \pm SD	2.48 \pm 1.38	5.66 \pm 1.75	6.50 \pm 1.31	12.244* (0.002)
Median	3.00	5.35	7.10	
Z₁ (p)		3.081* (0.002)	2.501* (0.012)	
Z₂ (p)			0.716 (0.474)	
Control group				
Range	2.60-6.50	2.70-7.50	5.80-8.00	
Mean \pm SD	4.78 \pm 1.65	5.50 \pm 1.47	7.92 \pm 0.73	1.127 (0.569)
Median	5.00	5.25	7.95	
Z₁ (p)		0.922 (0.356)	0.107 (0.915)	
Z₂ (p)			0.815 (0.415)	
Z (p)	1.934 (0.053)	0.000 (1.000)	1.549 (0.121)	

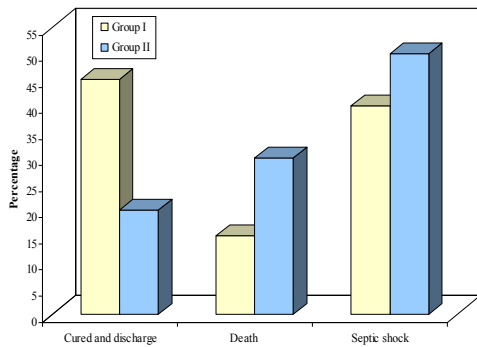


Figure 1. Comparison between the two studied groups according to prognosis and outcome at the end of the study.

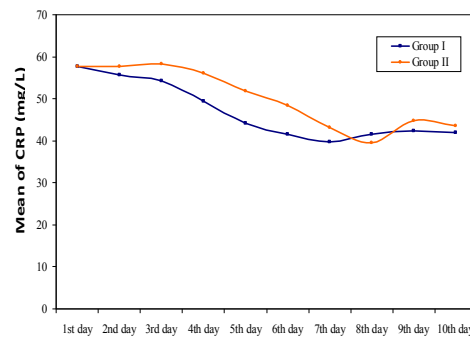


Figure 4. Comparison between the studied groups according to CRP along the course of the study.

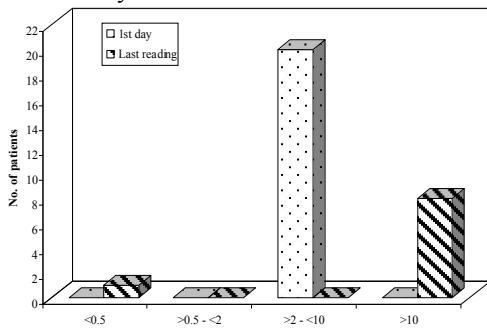


Figure 2. First and last read of PCT level along the course of the study in Statin Group.

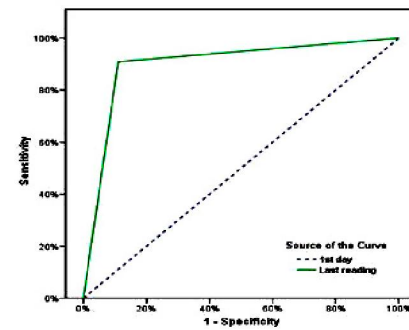


Figure 5. Receiver- operating-characteristic curve of PCT (Statin Group).

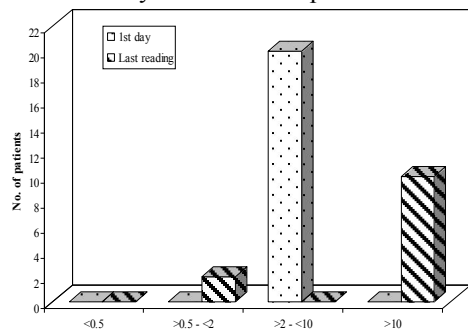


Figure 3. First and last read of PCT level along the course of the study in Control Group.

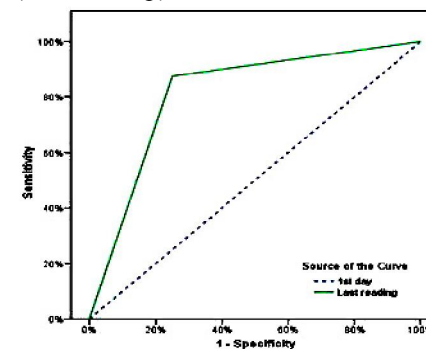


Figure 6. Receiver- operating-characteristic curve of PCT (Control Group).

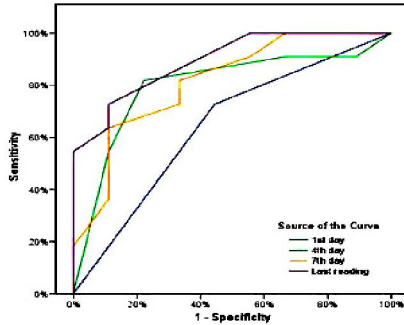


Figure 7. Receiver- operating-characteristic curve of CRP (Statin Group).

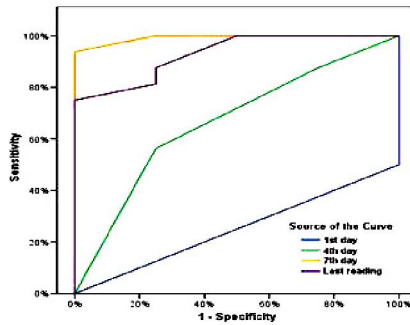


Figure 8. Receiver- operating-characteristic curve of CRP (Control Group).

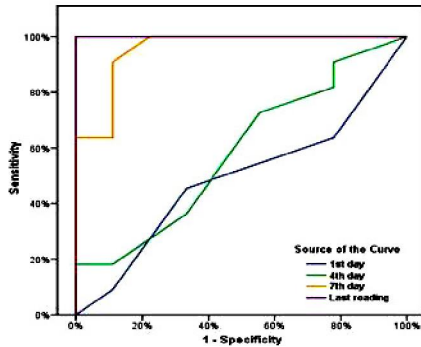


Figure 9. Receiver- operating-characteristic curve of SOFA score (Statin Group).

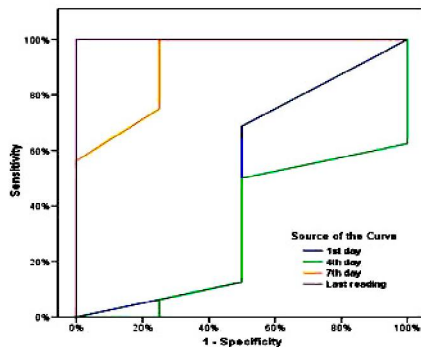


Figure 10. Receiver- operating-characteristic curve of SOFA score (Control Group).

In the present study, (57.5%) of the all studied patients were males, there was no significant difference among male and female patients who were admitted with sepsis in each group. This is contradicting with the results of Greg et al (12) who made a large epidemiological study on 750 million patients admitted due to sepsis, and showed that sepsis was more common among men than among women with significant association with males. This contradict can be explained by the small sample size of our study which is unsuitable for gaining accurate results concerning demography.

The present study showed that there was a decreased in the incidence of deterioration to sever sepsis and also mortality rate in the patients had history of DM and HTN in the statin group, than the patients in the control group, but it was non significant decrease. Which means that subsequent chronic diseases in our study didn't alter the significant effect of statin on sepsis's outcome, in either overall or attributable mortality rates. This goes with the results of Sethi et al (13) and Hackam et al. (8).

One of the potential uncontrolled confounders in this study was the administration of other treatment before admission to the ICU, there was no significant difference between patients who received or not received antibiotics before admission in each group or in between two groups as regard the prognosis and outcome. These results go with the results of Almog et al, (14) who made a study on 361 patients admitted with sepsis.

In relation to outcome of sepsis, statins lead to non significant decrease in the incidence of deterioration of early sepsis to sever sepsis and septic shock by about 10% in the statin group and non significant decrease in the mortality rate by about 15% in comparison to the non statin group.

The age of all the 40 studied patients ranged from 25 to 59 years. Patients aged under 19 or above 80 years were excluded from the study as they were considered as a high risk group. The study showed that there was no significant difference between the mean ages in between both groups in each outcome. There were significant differences between the mean ages of cured patients and sever septic and died patients in statin group. This goes with Reimar et al (11) who reported that the lowest relative death rate associated with statins was observed in older patients in those with bacteremia.

These data in our study go with the results of Reimar et al,(11) who made a study on 53 patients which showed that the statin group was associated with 30 % lower rate of sever sepsis, also with non significant different in the mortality rate between groups (about 9-10 %). And it goes with Hackam et

al and Redelmeier et al(8) in their large population-based cohort study, reported that in a large cohort of patients, those taking statins had a 19% reduction in the relative risk of severe sepsis compared with controls. The study also goes with Ahmed et al (15) and Thomsen et al (16) that mortality rate among statin users was lower than among non-users

In contradiction with our results, a large national prospective cohort study done by Rajesh et al,(17) where the statin use was associated with a large and statistically significant reduction in the incidence rate of severe sepsis about 63% lower in the statin group compared with the control group. Also the present study is contradicting with the results of Majumdar et al, (18) who reported that Statins are not associated with reduced mortality, and the benefit in the setting of sepsis by statins may be a result of confounding. The contradict may be explained by the small sample size and the short duration (10 days) of our study which is unsuitable for more follow up for gaining accurate results, after more complete adjustment for confounding.

In the present study the effect of statin administration during sepsis and the progression of the disease was evaluated and monitored by laboratory investigations. In the statin group along the course of the study, the WBC count decreased more than the control group, this goes with that of Weitz-Schmidt et al. (19) In opposite to the metabolic acidosis which increased but less than the control group. They showed no significant differences between both groups, as Reimar et al reported in his study.

The CRP level decreased significantly in both studied groups along the study duration. and significantly decreased more in the statin group at 4th and 5th day than the control group. This goes with the results of Jupiter study 2009, (20) Ridker et al (21) who reported in his study, that statins are associated with reductions in CRP levels.

PCT decreased more in the statin group than the control group but without significant decrease. and PCT levels were closely correlated with the sepsis and its subsequent developments from deterioration to death than the CRP. This goes with the results of Brunkhorst et al (22) in his study. Who found that PCT level can differentiate between SIRS, early sepsis, severe sepsis and septic shock. Also it goes with Canan et al, (10) who found that PCT level increased in parallel with the severity of the clinical condition of the patient. Also it goes with Bettina et al, (23) who reported that persistently high concentration of procalcitonin greater than 10 ng/mL, was seen in the non-survivors. Procalcitonin kinetics can be used to assess the effectiveness of treatment

more than other parameters, this was demonstrated by BRAHMS PCT Assay 2008.

Our study also demonstrated that PCT exhibited a greater sensitivity, specificity than CRP in stratification of patients according to severity as regard the last reading at the end of the study in agreement with the outcome in each group. With respect to positive and negative predictive values, PCT markedly exceeded CRP. In the receiver-operating-characteristic (ROC) curve, this documented that the PCT was a good predictor than CRP in relation to mortality. This goes with the results of Canan et al, (10) Simon et al (24) and Rey et al (25) in their prospective observational studies. They stated that PCT appeared to be a more accurate parameter, and had the highest sensitivity and specificity (85%-91% respectively) in comparison to CRP (58% -59%).

In the present study, the mean of SOFA score of statin group increased but at a lower rate than control Group with no significant difference between the two studied groups during the study duration. And the receiver operating characteristic curve (ROC) demonstrated the good sensitivity of SOFA score along the course of the study during staying in the ICU till the end of the study, which reached about 100% in both groups. Also showed the highest mean SOFA score correlated well with deterioration of the disease at mean ≥ 5.50 and with mortality at a mean ≥ 6.50 , so the mean SOFA score was a useful predictor of outcome and mortality rate. This goes with the results of Ferreira et al result, (26) and Vincent et al.(27)

In the studied patients, the GCS done as a daily clinical assessment of the level of consciousness and status of the central nervous system during the course of the study. And also needed as a part of the scoring system (SOFA Score). The GCS decreased along the course of the study in both groups, control group showed successive significant decrease than the statin group till the end of the study.

The result of this study showed the good effect of using statins as adjuvant therapy in the management of patients with sepsis in addition to their lipid lowering properties, and their effect in decreasing the worse deterioration of sepsis and the mortality rate.

5- Conclusions

1. Statins can be used as a good adjuvant therapy of sepsis in addition to their lipid lowering properties.
2. Statins decrease the worse deterioration of sepsis and the mortality rate but without significant values.

3. PCT is an accurate diagnostic parameter for sepsis, closely correlates with the sepsis and its subsequent deterioration than CRP.
4. Potential confounders such as anti biotic pre-administration which may differed in between groups, have to be more controlled.
5. Serial evaluation of the PCT level allowing more accurate diagnosis and follow up of sepsis.
6. The limitation of this study is that, the potential role of statins in the treatment of sepsis should be further evaluated in a large prospective randomized controlled studies.

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