How to Cite:
Mostafa, A. M. H., Noh, N. G. E., Nashed, S. W., Sersy, M. H. E., & Mohamed, M. Y. (2021). The role of statins in early sepsis in post cardiac surgery. *International Journal of Health Sciences*, *5*(S2), 1313–1326. https://doi.org/10.53730/ijhs.v5nS2.14669

The role of statins in early sepsis in post cardiac surgery

Ahmed Mohammed Hassan Mostafa
Consultant of intensive care medicine national heart institute
Corresponding author email: Ahm_hassan79@yahoo.com

Nehal Gamal Eldin Noh
Professor of Anesthesia and Critical Care Medicine, Faculty of Medicine, Ain shams University

Sheirf Wadie Nashed
Professor of Anesthesia and Critical Care Medicine, Faculty of Medicine, Ain shams University

Mayar Hassan El Sersy
Lecturer of Anesthesia and Critical Care Medicine, Faculty of Medicine, Ain shams University

Mohamed Yosef Mohamed
Lecturer of Anesthesia and Critical Care Medicine, Faculty of Medicine, Ain shams University

***Abstract*---**Background: Sepsis is a condition where the body's immune system overreacts to an infection, leading to a widespread inflammatory reaction. Present therapeutic endeavors predominantly concentrate on medications that have the ability to obstruct stages within the inflammatory cascade. Objective: This study sought to examine the influence of statin medication on early sepsis, with a focus on its pleiotropic effects and prognostic implications. A total of fifty patients diagnosed with early sepsis were included in the study. These patients were admitted to the critical care departments of Ain Shams University and the National Heart Institute between February 2012 and February 2013. The patients were categorized into two cohorts: the statins group, which consisted of individuals undergoing heart surgery and getting a daily dose of 80 mg of atorvastatin for four consecutive days, in addition to traditional sepsis therapy; and the control group, which only received conventional sepsis therapy. Results: The results showed that a brief period of intense statin medication led to a considerable decrease in levels of C-reactive protein (CRP) and procalcitonin (PCT) by day 4. Although there was no

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2021.
Manuscript submitted: 27 Sept 2021, Manuscript revised: 09 Nov 2021, Accepted for publication: 18 Dec 2021

significant decrease in nitric oxide (Nox) levels, the total cholesterol levels remained unchanged. In addition, the use of statin medication resulted in a notable decrease in the occurrence of severe sepsis, as seen by a reduction in both the average and highest Sequential Organ Failure Assessment (SOFA) scores. While not reaching statistical significance, the use of statin medication shown tendencies towards decreasing the requirement for mechanical breathing and vasopressors. The therapy was considered safe in terms of liver enzymes, myositis, and rhabdomyolysis. Conclusion: Administering a brief, intense course of atorvastatin at a dosage of 80 mg per day for four consecutive days shows potential as an effective additional treatment for early sepsis.

***Keywords*---**early sepsis, statin therapy, atorvastatin, inflammatory response, prognostic implications.

Introduction

Sepsis is an intricate and potentially fatal illness marked by an unbalanced immune response to infection, resulting in organ failure[1]. Despite thorough investigation and medical treatments, sepsis continues to be a significant worldwide health issue with elevated rates of illness and death[2]. Prompt detection and efficient treatment of sepsis are vital to enhance patient results[3]. There has been an increasing interest in the possible immunomodulatory effects of statins, which are routinely used to reduce cholesterol levels[4]. Statins, like atorvastatin, have demonstrated anti-inflammatory and pleiotropic effects that go beyond their main function of reducing cholesterol levels[5].

Early sepsis following heart surgery refers to a particular subgroup of sepsis that presents distinct challenges and requires appropriate precautions[6]. Cardiac surgery patients are prone to infections, and it is crucial to promptly start appropriate therapies[7]. The role of statins in the context of early sepsis following heart surgery is a topic that is gaining attention and necessitates thorough investigation[8] .The HMG-coA reductase inhibitors, also known as "statins", are already widely prescribed[9]. Statins are a leading approach to managing dyslipidemia and play a crucial role in preventing cardiovascular disease, which is a major problem in Western societies[10].

Currently, Statins hold the highest rate of prescription of several pharmaceutical tablets[11]. In January 2006, the National Institute for Health and Clinical Excellence (NICE) stated that statins should be prescribed to people for both secondary prevention and primary prevention if they have a risk greater than 20% of acquiring cardiovascular disease during the next 10 years[12] .Gaining insight into the impact of statins in early sepsis not only aids to the ongoing development of sepsis management but also offers essential understanding of the potential multiple effects of these drugs.

The objective of this study is to examine the effects of a brief but intense treatment with the statin drug atorvastatin on the occurrence of early sepsis in

patients who have undergone heart surgery. We want to investigate the possible advantages and safety of using statin medication as an additional treatment in the initial phases of sepsis following heart surgery by analyzing inflammatory markers, organ dysfunction ratings, and clinical outcomes.

Method

Study design
Research Methodology

This study utilized a prospective, randomized clinical trial to examine the effects of short-term, high-intensity statin medication on early sepsis in patients who underwent heart surgery. The study sample comprised 50 patients, with an equal distribution of 25 individuals in each group: the Statins Group and the Control Group.

1. Group of Statins: Enrolled 25 patients who underwent heart surgery and experienced early sepsis. Administered statin treatment, namely a daily dose of 80 mg of atorvastatin for four consecutive days. Simultaneously had standard treatment for sepsis.
2. Experimental Group: The study comprised a cohort of 25 individuals who underwent heart surgery and subsequently developed early sepsis. Patients received standard sepsis treatment only.

Every patient was closely observed and assessed from the first day until the day they were released from the intensive care unit (ICU).

Assessment of the Patient

Comprehensive Clinical Assessment

The evaluation of vital signs, such as blood pressure, temperature, respiration rate, heart rate, central venous pressure (CVP), and urine output (UOP), will be performed upon admission and on a regular basis afterward.

Laboratory Investigations

- Standard laboratory tests were undertaken including CBC, Prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- Liver Function Tests including ALT, AST, Bilirubin, and albumin.
- Kidney Function Tests including Urea, Creatinine, Sodium, and Potassium.
- Creatinine Phosphokinase (CPK).
- Lipid Profile: Total cholesterol and triglycerides.
- Inflammatory Markers: CRP (C-reactive protein), PCT (Procalcitonin), and NO (Nitric oxide).
- These labs were conducted on day 1 and repeated on day 4 after the last dose of

Microbiological Studies

Pan cultures, including sputum, blood, urine, and other biological fluids, were obtained before the administration of antibiotics or after discontinuation of antibiotics for 48 hours.

Clinical Data

The duration of patients' stay in the intensive care unit (ICU), the ultimate result, and the requirement for organ supporting interventions such as vasopressors, mechanical ventilation, and hemodialysis were documented for all patients until they were discharged from the ICU.

Imaging Studies

Chest X-ray and ultrasound were utilized to identify the source of sepsis.

Scoring System

The Sequential Organ Failure Assessment (SOFA) score was administered on the day of admission and subsequently each day until ICU release. SOFA ratings were derived for respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems.

Patients

Our study comprised 50 patients who were admitted to the surgical ICU and acquired sepsis during their stay, meeting the inclusion criteria.

Inclusion and Exclusion Criteria

Criteria for Inclusion

Patient must be an adult who fulfilling the criteria for sepsis according to the ACCP/SCCM criteria which include infection that is either suspected by the treating physician based on clinical observations or confirmed through diagnostic tests. Otherwise, two or more of the following: The temperature is either 38ºC (100.4°F) or 36ºC (96.8°F), the heart rate is greater than 90 beats per minute, the respiratory rate is greater than 20 breaths per minute or the PaCO2 is less than 32mmHg, and the white blood cell count is either greater than 12,000/mm3 or less than 4000/m3, or there is more than 10% immature neutrophils. Patients who had initial sepsis occurring within 24 hours following the manifestation of sepsis criteria.

Criteria for exclusion

Patients with the following criteria were excluded from participation. Patients who are in Gestation and patients who have ALT level that is more than three times higher than the upper limit of the normal range. In addition; patients who have level of creatine phosphokinase (CPK) which is much higher than the upper limit

of normal. Patients who have prior medical record of allergic reactions or sensitivity to statins. Patients presenting with severe sepsis, multiple organ dysfunction (MOD), or septic shock upon arrival and patients discharged from the ICU against medical recommendation, with pending or lost investigations and lack of patient follow-up. Finally, patient who is now receiving statins medication before to surgery.

Statistical analysis

The study employed IBM SPSS statistics software to analyze the data. The quantitative parametric measures were presented as mean ± standard deviation, while the non-parametric measures were presented as median percentiles. Categorized data was shown as both the number and percentage. The following tests were conducted: the Wilcoxon Rank Sum test for non-parametric data, the Ranked Sperman correlation test for non-parametric data, and the Chi-square test for classified data. The significance level was established at 0.05, with a likelihood of error of 0.01 and 0.001 being considered extremely significant.

Results

Demographic data

Both groups were compared as regard Gender & Age and risk factors include (HTN, DM, Renal impairment & CAD) and also source of sepsis & show no significant difference between two groups. Table (1)

Table (1) Demographic data in both groups

	Case	Control	P Value
Males	13 (52%)	14 (44%)	0.77
Females	12 (48%)	11 (56%)	
Age	49.2 ± 14.2	49.5 ± 12.8	0.94
DM	12 (48%)	11 (44%)	0.78
HTN	13 (52%)	14 (56%)	0.77
CAD	14 (56%)	15 (60%)	0.74
Renal impairment	8 (32%)	4 (16%)	0.18

Cultures were obtained from both groups and the results indicate: The statins group exhibited infections in many areas of the body, with the majority occurring in the chest (56%), followed by the blood (12%), mediastinum (12%), and wounds (20%). The responsible organisms were Acenitobacter (28%), dephteroids (4%), Klebsilla (28%), MRSA (16%), and pseudomonas (24%). The control group consisted of blood samples (12%), chest samples (60%), mediastinum samples (16%), and wound samples (12%). The causal organisms identified were Acenitobacter (32%), dephteroids (0%), Klebsilla (24%), MRSA (16%), and pseudomonas (28%).

Pleiotropic effect of statins

The anti-inflammatory and pleiotropic effect of statins can be determined by the following markers presented in Table (2)

Table (2) Mean ± SD of C reactive protein level, Procalcitonine level and Nitric oxide level at day1 & day 4 in both groups

Markers	Case	Control	P value
CRP Day 1	55.9 ± 32.8	54.1 ± 26.6	0.84
CRP Day 4	33.3 ± 22.9	51.9 ± 24.1	0.007 *
PCT Day 1	0.64 ±0.16	0.64 ± 0.17	0.85
PCT Day 4	0.44 ± 0.11	0.60 ± 0.15	0.001 *
No Day 1	57.8 ± 9.9	60 ± 8.8	0.412
No Day 4	56.4 ± 10.3	61.5 ± 8.5	0.063

The study compared the average levels of CRP, Procalcitonin, and Nitric oxide in both groups on day 1 and day 4. The average CRP level was similar in both groups and higher than the usual range. On day 4, the CRP level dropped more pronounced in the statins group, with a statistically significant difference (*P*-vlaue 0.001). The average procalcitonin level was similar in both groups and higher than the normal range. On the fourth day, the statins group showed a significant reduction in PCT levels compared to the control group. The average NO level at admission fell in the statins group but not in the control group, with no statistically significant decline.

The initial SOFA score was assessed in each patient at admission, and thereafter, the daily SOFA score was used to determine the mean and highest SOFA scores in both groups. Upon comparing the initial SOFA score between the two groups upon admission, no statistically significant difference was seen (*P*-value 0.87). This indicates that both groups exhibited similar severity of illness upon admission. During the hospital course, there was a notable disparity between the two groups, with the statins group demonstrating a favorable outcome in terms of mean SOFA (*P*-value 0.038) and highest SOFA (*P*-value 0.043). (Table 3, Figure 1)

Table (3): Median & IQR of initial, Mean, highest SOFA scores in both groups

	Case	IQR	Control	IQR	P Value
Initial SOFA	4	2 - 5	4	2 - 5	0.87
Mean SOFA	3	1 - 7.5	4.2	1.3 - 6.9	0.038 *
Highest SOFA	4	2 - 12	6	2 - 19	0.043 *

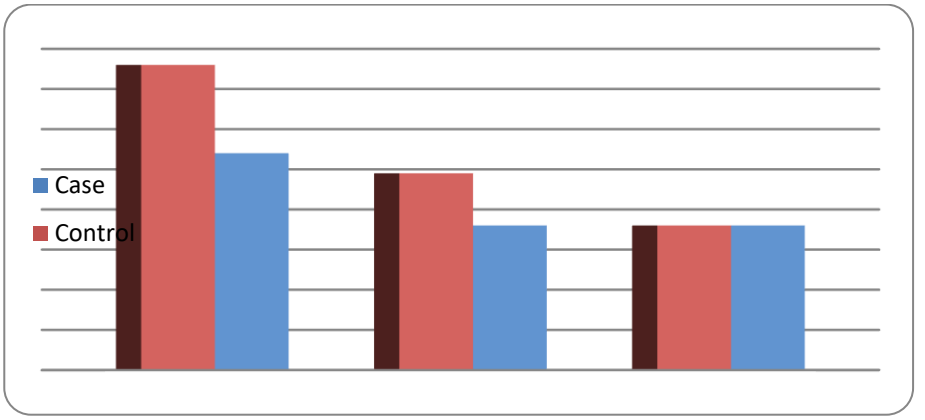

Fig. (1): Initial, Mean, highest SOFA scores in both groups

The initial SOFA score was assessed in each patient at admission, and thereafter, the daily SOFA score was used to determine the mean and highest SOFA scores in both groups. Upon comparing the initial SOFA score between the two groups upon admission, no statistically significant difference was seen (*P*-value 0.87). This indicates that both groups exhibited similar severity of illness upon admission. During the hospital course, there was a notable disparity between the two groups, with the statins group demonstrating a favorable outcome in terms of mean SOFA (*P*-value 0.038) and highest SOFA (*P*-value 0.043).

The impact of statins on the clinical progression can be assessed by evaluating the requirement for organ supportive interventions, such as the demand for vasopressors (VC), mechanical ventilation (MV) and hemodialysis (HD). Upon comparing both groups in terms of the requirement for organ supportive measures, we observed no significant difference in reducing the need for mechanical ventilation (*P*-value 0.569) and the need for hemodialysis (P Value 0.713). However, the group receiving statins exhibited a non-significant decrease in the need for vasopressors compared to the non-statin group (P Value 0.087).

Table (4): The need for organ supportive measures

	Case	Control	P Value
Vasopressor	11 (44%)	17 (68%)	0.087
M.V	13 (52%)	15 (60%)	0.569
H.D	5 (20%)	4 (16%)	0.713

Length of ICU stay

The group receiving statins exhibited a noteworthy reduction in the duration of their stay in the intensive care unit compared to the group not receiving statins (P Value 0.021). Table (5)

Table (5): Length of ICU

	Case	Control	P Value
Length of ICU stay (in days)	12 ± 7.1	14.12 ± 5.9	0.021 *

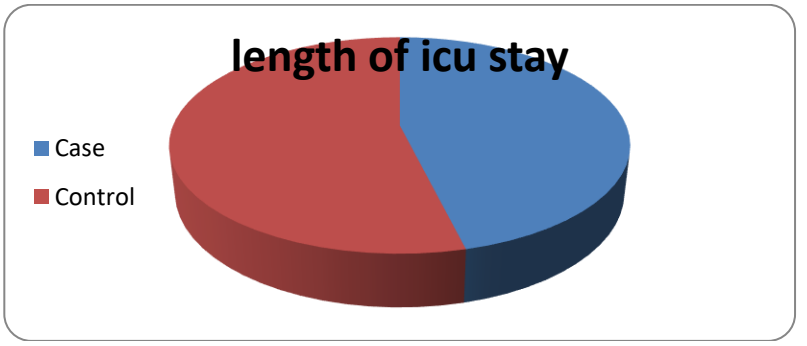

Fig. (2): Length of ICU stay

Final outcome

The mortality rate in the group receiving statins was lower (40%) compared to the control group (48%). However, this difference did not reach statistical significance (P value 0.56).

Table (6): Mortality in both groups

	Case	Control	P Value
Mortality	10 (40%)	12 (48%)	0.569

Safety of statins

The safety of statins was evaluated by regularly measuring liver and muscle enzymes throughout the research duration. The serial measurement of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in both the statins group and the control group revealed a negligible increase from the initial readings, with a p-value of 0.128 for ALT and 0.161 for AST, respectively. The serial measurement of creatine phosphokinase (CPK) in both the statins and control groups revealed a negligible increase from the initial values, which was not statistically significant (P Value 0.9). (Figure 3, 4. Table 7)

Table (7): ALT on admission and day

	Case	Control	P Value
ALT Adm	22.48 ± 9.7	22.1 ± 11.5	0.9
ALT 4	28.36 ± 9.7	33.2 ± 17.3	0.128
AST Adm	22.68 ± 9.2	25.28 ± 9.2	0.327
AST 4	29.76 ± 10.8	36.1 ± 19.5	0.161
	Case	Control	P Value

CPK Adm	107.2 ± 61.2	103.5 ± 53.9	0.8
CPK 4	107.5 ± 48.8	107.4 ± 60.2	0.9

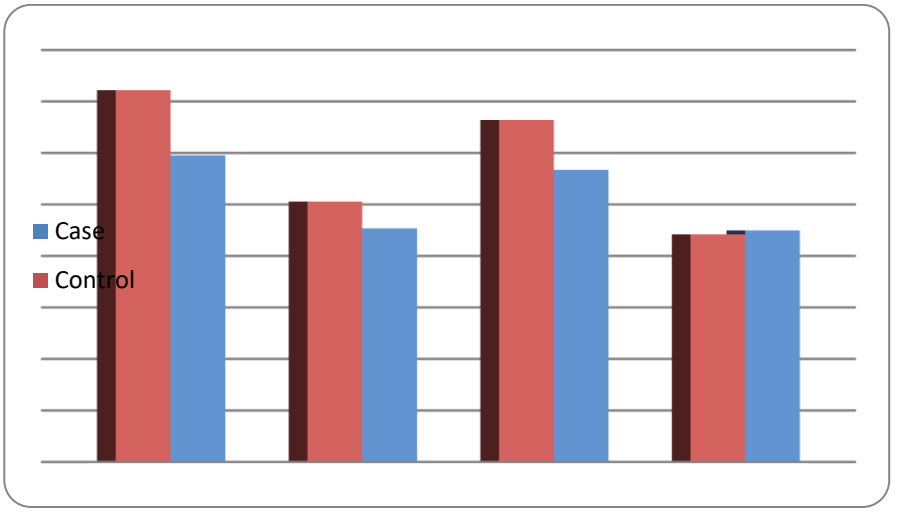

Fig. (3) ALT & AST on day 1 & day 4 in both groups

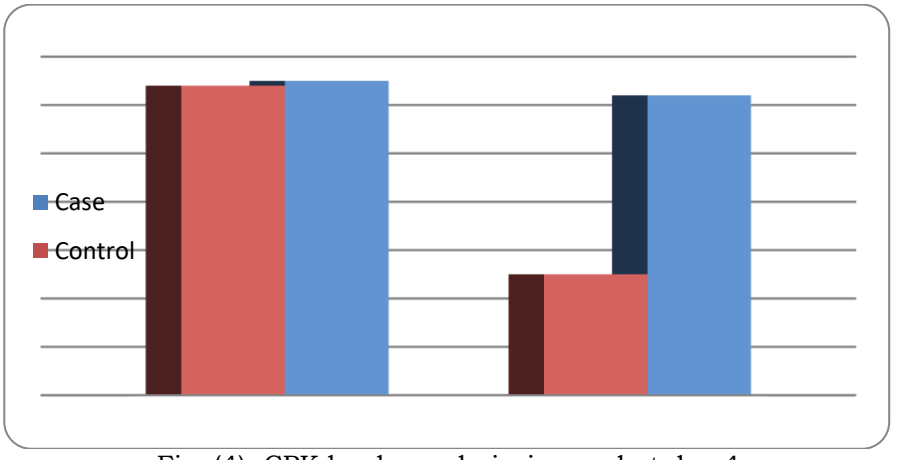

Fig. (4): CPK level on admission and at day 4

Discussion

Sepsis, as defined by a consensus conference, is a condition characterized by a systemic inflammatory response syndrome that develops during an infection[13]. It is commonly understood to be a disease that is worsened by the incorrect immune response in the affected person[14]. Both fundamental research and clinical trials have concentrated on identifying agents that can effectively inhibit specific stages of the inflammatory cascade.

Nevertheless, among the various therapeutic approaches examined, only activated protein C and low dose hydrocortisone have been shown to be beneficial for patients with sepsis in terms of controlling inflammation[15]. HMG-CoA reductase

is an enzyme that plays a role in the production of cholesterol. Statins suppress the activity of this enzyme, resulting in a decrease in cholesterol levels[16.] In addition to reducing cholesterol levels, statins have demonstrated pleiotropic effects, such as possessing anti-inflammatory characteristics[17]. Research investigations have shown that statins have the ability to inhibit inflammatory reactions at the cellular level[18]. The anti-inflammatory actions of this substance can be ascribed to its ability to regulate many inflammatory pathways, including the suppression of pro-inflammatory cytokines[19].

The average CRP level on day 1 was similar in both groups and much higher than the normal range, which can be attributed to sepsis. The average level of CRP on day 4 reduced in both groups, but it was lower in the statins group compared to the control group. This decrease was statistically significant, with a P value of 0.007. The average level of procalcitonin (PCT) on day 1 was similar in both groups, and it was higher than the normal range. This elevation can be attributed to sepsis. On the fourth day, the group receiving statins exhibited a notable reduction in PCT levels compared to the control group (P Value 0.001).

Magrini L.et al.[20] conducted a study to assess the diagnostic and prognostic use of procalcitonin (PCT) in individuals displaying indications of infections. The study included 261 participants. Upon arrival in the emergency department (ED), a procalcitonin (PCT) test was conducted (T0). Five days after receiving antibiotic therapy, another PCT test was performed (T5). The results showed that the average PCT value at T0 was 7.1±17.9ng/ml, while at T5 it was 3±9.1ng/ml (p <0.0001). These findings suggest that PCT is a valuable indicator for diagnosing both systemic and local infections. Additionally, it can be used to assess the prognosis of patients with acute infectious diseases upon their arrival in the ED. Notably, changes in PCT levels following antibiotic therapy are highly indicative of in-hospital mortality. Normalization of peripheral blood cell count (PCT) levels following antibiotic treatment indicates a favorable response to infection, potentially resulting in reduced mortality associated with the infection[20].

In 2012, Minoo Adib[21] and colleagues conducted a study to examine the usefulness of procalcitonin and C-reactive protein in diagnosing neonatal sepsis. The study involved 69 neonates who were suspected to have an infection. The patients were divided into two groups based on their clinical symptoms of sepsis, as well as bacteriological and laboratory findings. Group I comprised 20 newborns who tested positive for a blood infection, while Group II comprised 49 neonates who tested negative for a blood infection but displayed two or three clinical signs of sepsis. The results demonstrate that the average levels of procalcitonin and CRP were significantly higher in septic neonates (Group I) compared to the other two groups (P< 0.005). Therefore, this study suggests that procalcitonin is a more effective marker than CRP for diagnosing neonatal sepsis.[21]

A 2019 meta-analysis by Tan M, et al.[22] assessed the clinical utility of procalcitonin and C-reactive protein in diagnosing sepsis in adult patients. The study involved nine trials, with 495 sepsis patients and 873 nonsepsis patients. The diagnostic accuracy of C-reactive protein (CRP) for sepsis was found to be 0.73, with sensitivity and specificity of 0.80 and 0.61 respectively. The diagnostic odds ratio (DOR) was calculated to be 6.89. Procalcitonin (PCT) also showed good

diagnostic accuracy, with sensitivity and specificity of 0.80 and 0.77 respectively. The DOR was 12.50, with a confidence interval of 3.65-42.80. Both tests have shown good accuracy in diagnosing sepsis.[22]

Our study also investigated the level of Nitric oxide (NO) and found that early treatment of sepsis with statins can potentially lower the level of NOx. However, the reduction was not statistically significant. Specifically, we compared the mean level of NOx upon admission in both groups and found that it was elevated above the normal range (P Value 0.412), which can be attributed to sepsis. The average NOx level on day 4 reduced in the group treated with statins, but not in the control group. However, this reduction was not statistically significant (P Value 0.063). It can be attributed to the effect of atorvastatin on endothelial cells, which is a pleiotropic action of statins.

According to Santos SS.et al.[23], a study was conducted to assess the production of reactive oxygen species (ROS) and nitric oxide (NOx) in septic patients and its correlation with clinical outcomes. The study involved 49 septic patients and 19 healthy volunteers. The findings revealed that septic patients had higher levels of nitric oxide production compared to healthy volunteers. Furthermore, the persistence of these elevated levels was found to be linked to unfavorable clinical outcomes[23].

In our study, we investigated the impact of early statins therapy on decreasing the incidence of severe sepsis. Our findings revealed a decreased risk of developing severe sepsis, as evidenced by comparing the Sequential Organ Failure Assessment (SOFA) score and clinical progression during the stay in the Intensive Care Unit (ICU). Specifically, we compared the initial SOFA score between the two groups upon admission and found no statistically significant difference (P Value 0.87). This indicates that both groups had a similar level of illness severity upon admission. Throughout the hospital course, there was a notable disparity between the two groups, with the statins group demonstrating a more favorable outcome, as seen by the mean Sequential Organ Failure Assessment (SOFA) score (P Value 0.038) and the highest SOFA score (P Value 0.043).

The meta- analysis of Pertzov B, et al [24] revealed that fourteen trials, which involved a total of 2628 participants. The use of statins did not result in a decrease in 30-day all-cause mortality for both all patients (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.83–1.10) and a subgroup of patients with severe sepsis (RR 0.97, 95% CI 0.84–1.12). The level of assurance regarding both results was strong. The rate of adverse events did not differ across the trial arms (RR 1.24, 95% CI 0.94 to 1.63). The level of assurance regarding the evidence for this outcome was strong.[24]

The present study investigated the impact of early statins therapy on reducing mortality rate. Our findings revealed a statistically non-significant decrease in mortality among the statins group, with a mortality rate of 40% compared to 48% in the control group. However, this difference did not reach statistical significance (P value 0.569).

In the study of Park J, et al. [25] The statin group exhibited significantly lower 1-year and overall mortalities compared to the no statin group, with rates of 6.1% versus 13.3% (hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.41–0.74; $p < 0.001$) for 1-year mortality and 15.0% versus 25.0% (HR, 0.62; 95% CI, 0.51–0.76; $p < 0.001$) for overall mortality. Analyses following inverse probability treatment weighting yielded similar results (HR, 0.61; 95% CI, 0.50–0.74; $p < 0.001$ for 1-year mortality and HR, 0.70; 95% CI, 0.54–0.90; $p = 0.006$ for overall mortality). Notably, mortalities did not show significant differences based on the statin dose. These findings suggest a potential association between statin treatment and improved survival following MINS. However, it is crucial to emphasize the need for a trial to confirm these observations and establish causality.

Conclusion

A high-dose treatment plan for early sepsis, focusing on Atorvastatin at 80 mg per day for four consecutive days, has been suggested as an effective treatment due to its anti-inflammatory benefits and reduced occurrence of severe sepsis. The treatment regimen is safe for liver and muscle enzymes, highlighting the potential of short-term statin medication in managing early sepsis.

Conflict of interest: None
Funding: None

References

1. Lelubre C, Vincent JL. Mechanisms and treatment of organ failure in sepsis. Nature Reviews Nephrology. 2018 Jul;14(7):417-27.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020 Jan 18;395(10219):200-11.
3. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, Lemeshow S, Osborn T, Terry KM, Levy MM. Time to treatment and mortality during mandated emergency care for sepsis. New England Journal of Medicine. 2017 Jun 8;376(23):2235-44.
4. Dehnavi S, Sohrabi N, Sadeghi M, Lansberg P, Banach M, Al-Rasadi K, Johnston TP, Sahebkar A. Statins and autoimmunity: State-of-the-art. Pharmacology & Therapeutics. 2020 Oct 1;214:107614.
5. Liberale L, Carbone F, Montecucco F, Sahebkar A. Statins reduce vascular inflammation in atherogenesis: a review of underlying molecular mechanisms. The international journal of biochemistry & cell biology. 2020 May 1;122:105735.
6. La Russa R, Maiese A, Di Fazio N, Morano A, Di Bonaventura C, De Matteis A, Fazio V, Frati P, Fineschi V. Post-traumatic meningitis is a diagnostic challenging time: a systematic review focusing on clinical and pathological features. International Journal of Molecular Sciences. 2020 Jun 10;21(11):4148.

7. Silva QC, Barbosa MH. Risk factors for surgical site infection in cardiac surgery. Acta Paulista de Enfermagem. 2012;25:89-95.
8. Clark LL, Ikonomidis JS, Crawford Jr FA, Crumbley III A, Kratz JM, Stroud MR, Woolson RF, Bruce JJ, Nicholas JS, Lackland DT, Zile MR. Preoperative statin treatment is associated with reduced postoperative mortality and morbidity in patients undergoing cardiac surgery: an 8-year retrospective cohort study. The Journal of Thoracic and Cardiovascular Surgery. 2006 Mar 1;131(3):679-85.
9. Markowska A, Antoszczak M, Markowska J, Huczyński A. Statins: HMG-CoA reductase inhibitors as potential anticancer agents against malignant neoplasms in women. Pharmaceuticals. 2020 Nov 25;13(12):422.
10. Writing Committee, Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD, DePalma SM, Minissian MB, Orringer CE, Smith SC. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. Journal of the American College of Cardiology. 2016 Jul 5;68(1):92-125.
11. Yeh JS, Franklin JM, Avorn J, Landon J, Kesselheim AS. Association of industry payments to physicians with the prescribing of brand-name statins in Massachusetts. JAMA internal medicine. 2016 Jun 1;176(6):763-8.
12. National Institute for health and Clinical Excellence. Technology Apprasial 94: Statins for the prevention of cardiovascular events. NHS, January 2006.
13. Salomão R, Ferreira BL, Salomão MC, Santos SS, Azevedo LC, Brunialti MK. Sepsis: evolving concepts and challenges. Brazilian Journal of Medical and Biological Research. 2019 Apr 15;52:e8595.
14. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, Fine J, Krichevsky A, Delude RL, Angus DC, GenIMS Investigators. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Archives of internal medicine. 2007 Aug 13;167(15):1655-63.
15. Meduri GU, Annane D, Confalonieri M, Chrousos GP, Rochwerg B, Busby A, Ruaro B, Meibohm B. Pharmacological principles guiding prolonged glucocorticoid treatment in ARDS. Intensive care medicine. 2020 Dec;46:2284-96.
16. Gesto DS, Pereira CM, Cerqueira NM, Sousa SF. An atomic-level perspective of HMG-CoA-reductase: The target enzyme to treat hypercholesterolemia. Molecules. 2020 Aug 26;25(17):3891.
17. Mohammad S, Nguyen H, Nguyen M, Abdel-Rasoul M, Nguyen V, Nguyen CD, Nguyen KT, Li L, Kitzmiller JP. Pleiotropic effects of statins: untapped potential for statin pharmacotherapy. Current vascular pharmacology. 2019 May 1;17(3):239-61.
18. Kouhpeikar H, Delbari Z, Sathyapalan T, Simental-Mendía LE, Jamialahmadi T, Sahebkar A. The effect of statins through mast cells in the pathophysiology of atherosclerosis: a review. Current Atherosclerosis Reports. 2020 May;22:1-8.
19. Conti PR, Ronconi G, Caraffa AL, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-

inflammatory strategies. J Biol Regul Homeost Agents. 2020 Mar 1;34(2):327-31.
20. Magrini L, Travaglino F, Marino R, Ferri E, DE BERARDINIS B, Cardelli P, Salerno G, DI SOMMA S. Procalcitonin variations after Emergency Department admission are highly predictive of hospital mortality in patients with acute infectious diseases. European Review for Medical & Pharmacological Sciences. 2013 Feb 2;17.
21. Adib M, Bakhshiani Z, Navaei F, Fosoul FS, Fouladi S, Kazemzadeh H. Procalcitonin: a reliable marker for the diagnosis of neonatal sepsis. Iranian journal of basic medical sciences. 2012 Mar;15(2):777.
22. Tan M, Lu Y, Jiang H, Zhang L. The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: A systematic review and meta-analysis. Journal of cellular biochemistry. 2019 Apr;120(4):5852-9.
23. Santos SS, Brunialti MK, Rigato O, Machado FR, Silva E, Salomao R. Generation of nitric oxide and reactive oxygen species by neutrophils and monocytes from septic patients and association with outcomes. Shock. 2012 Jul 1;38(1):18-23.
24. Pertzov B, Eliakim-Raz N, Atamna H, Trestioreanu AZ, Yahav D, Leibovici L. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) for the treatment of sepsis in adults–a systematic review and meta-analysis. Clinical Microbiology and Infection. 2019 Mar 1;25(3):280-9.
25. Park J, Kim J, Lee SH, Lee JH, Min JJ, Kwon JH, Oh AR, Seo W, Hyeon CW, Yang K, Choi JH. Postoperative statin treatment may be associated with improved mortality in patients with myocardial injury after noncardiac surgery. Scientific Reports. 2020 Jul 15;10(1):11616.