Effects of simvastatin in abdominal sepsis in rats[1]

Efeitos da sinvastatina na sepse abdominal em ratos

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ABSTRACT

Purpose: Statins are widely recognized as hypolipemic drugs, but some studies have observed anti-inflammatory and immunomodulatory effects, known as pleiotropic. The aims of this work was to study possible anti-inflammatory effects of simvastatin in abdominal sepsis. Serum pro-inflammatory cytokines and leukocytes count were determined in an experimental model of abdominal sepsis, using cecal ligation and puncture (CLP) in rats. **Methods**: Twenty eigth Wistar rats weighing 285±12g were randomly divided in: CLP/Sinvastatin rats (n=7), treated with 10 mg/Kg of oral simvastatin 18 and 2 hs berofe CLP; CLP/Saline group rats (n=7), treated with oral saline; group Sham/Simvastatin (n=7), treated with simvastatin, and group Sham/Saline (n=7), treated with saline. Serum TNF-α, IL-1β and IL-6 by ELISA and total leukocytes, neutrophils, lymphocytes, and eosinophils were determined 24 hs after CLP. ANOVA and Tukey test were used considering significant $p<0.05$. **Results**: It was demonstrated that serum TNF-α, IL-1β and IL-6 were respectively 364,8±42pg/mL; 46,3±18pg/mL and 28,4±13pg/mL in CLP/Sinvastatin rats, significantly lower ($p<0.05$) than in group CLP/Saline (778,5±86pg/ml; 176,9±46pg/ml; 133,6±21 pg/ml, respectively). The same results were observed in total leukocytes and neutrophils counts. **Conclusion**: These results clearly demonstrate that simvastatin is an effective agent that reduces cytokines levels and leukocyte count in sepsis, independently of its well-known lipid-lowering effects. Thus, HMG-CoA reductase inhibitors like simvastatin have important anti-inflammatory effects in abdominal sepsis in rats.

Key words: Statin. Inflammation. Abdominal sepsis. Wistar rat. Cytokine. Leukocyte.

RESUMO

Objetivo: As estatinas são agentes reconhecidamente hipolipemiantes. Vários estudos têm revelado que eles têm ações pleiotrópicas, como antiinflamatória e imunomoduladora. Tentando-se entender o papel antiinflamatório da sinvastatina na sepse, foram analisados os níveis de citocinas pró-inflamatórias e contagem de leucócitos em modelo de sepse abdominal por ligadura e punção do ceco (LPC) em ratos**. Métodos**: Foram utilizados 28 ratos *Wistar* pesando 285±12g, assim divididos: grupo sepse (n=14), submetidos a LPC e grupo *sham* (n=14), submetidos a laparotomia e manipulação suave do ceco. No grupo LPC/sinvastatina (n=7) os ratos receberam 10mg/kg de sinvastatina via oral 18 e 2 horas antes da LPC e no grupo LPC/salina (n=7) os ratos receberam injeção oral de solução salina 0,9 %. Os animais dos grupos *sham*/sinvastatina (n=7) e sham/salina (n=7) receberam o mesmo tratamento. Dosagem de TNF-α, IL-1β e IL-6 por ELISA e contagem de leucócitos totais, neutrófilos, linfócitos e eosinófilos foram realizadas em todos os animais. Análise estatística foi feita pelo ANOVA e teste de Tukey, com significância $p<0,05$. **Resultados**: Ficou demonstrado que as dosagens de TNF-α, IL-1β e IL-6 atingiram valores de 364,8±42pg/ml; 46,3±18pg/ml e 28,4±13pg/ml no grupo submetido à sepse e tratados com sinvastatina, significantemente mais baixos do que no grupo sepse não tratados (778,5±86pg/ml; 176,9±46pg/ml; 133,6±21 pg/ml, respectivamente). O mesmo ocorreu na contagem de leucócitos totais e neutrófilos. **Conclusão**: A sinvastatina mostrou ação anti-inflamatória em ratos *Wistar,* diminuiu níveis de citocinas e leucócitos, sugerindo uso potencial na prevenção ou atenuação dos efeitos da sepse abdominal.

Descritores: Estatina. Inflamação. Sepse abdominal. Rato Wistar. Citocinas. Leucócitos.

Introduction

Statins are powerful hypolipemic drugs with pleiotropic effects and have been shown to improve survival in the primary and secondary prevention of atherosclerosis in numerous large randomized clinical trials[1,2]. By inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and the mevalonate pathway to cholesterol, statins reduce not only cholesterol but also the production of several of its nonsteroidal isoprenoid precursor intermediates[3], which are necessary to membrane anchor proteins critical to the binding of signaling proteins involved

in various cell functions. Several cellular and animal models demonstrate the pleiotropic activity of statins, including antiinflammatory and antioxidative properties, immunomodulatory effects, improvement in endothelial function, reduction in blood thrombogenicity, and increased nitric oxide (NO) bioavailability. Some or all of these effects may account for a substantial potential impact of statins on the complex pro and anti-inflammatory sequence of events occurring during sepsis. Extensive research has been invested in the last 2 decades and sepsis remains the leading cause of death among patients treated in intensive care units, with mortality rates ranging between 30% and 70%[4,5]. Sepsis is generally viewed as a disease aggravated by the inappropriate and inefficient immune response encountered in the affected individual. Corticosteroids[6,7], activated protein C[8], tumor necrosis factor (TNF) antagonists[9], interleukin-1 receptor antagonists[10], anti-endotoxin antibodies[11], and ibuprofen[12] have all been evaluated in a clinical setting, with improved outcome demonstrated recently for activated protein C. HMG-CoA reductase inhibitors (statins) such as simvastatin have been shown to exhibit important immunomodulatory effects independent of lipid lowering[13]. These pleiotropic effects have been demonstrated to include anti-inflammatory actions[14], improvement of endothelial and microvascular function, and modulation of endothelial nitric oxide synthase (eNOS)[15]. However, statins have thus far not been used to treat severe inflammatory states such as sepsis. Knowing that infection is an important risk factor to operated people and that statins have anti-inflammatory and antioxidant properties, we hypothesized that simvastatin pretreatment would be protective against abdominal sepsis in rats.

Methods

The experimental protocol was approved by the Research Ethics Committee of the University Hospital-UFRN, Brazil. Animals were handled in accordance with the Guide for the Care and Use of Laboratory Animals, US National Research Council, 1996.

Animals

Wistar rats weighing 285??6g were used. Rats were housed in polypropilene cages and maintained under controlled temperature conditions on a 12h light-dark cycle and allowed *ad libitum* access to commercially available rat chow (Labina, Purina®) and water.

Experimental design

A total of 28 Wistar rats were randomly distributed into the following four groups: In the sepsis group (n=14), a half of the (CLP/Sinvastatin) rats (n=7) received 10 mg/Kg of simvastatin microemulsion via gavage, 18 and 2 hours before cecal ligation and puncture (CLP). The remaining (CLP/Saline group) rats (n=7) were treated with oral injection of saline 18 and 2 hs before CLP. In the group sham, 7 rats were treated with simvastatin (Sham/Simvastatin group) and 7 with saline (Sham/Saline group) as sepsis group.

Surgical models

Animals were fasted 12 hr before the experiment and anesthetized with intramuscular injection of 0.1 mL/100g weight, of a solution prepared with 1.0 mL of ketamine (50mg/mL) and 1.0 mL of xilazine (20mg/mL). They breathed spontaneously throughout the procedures. After shaving, the abdominal skin was disinfected with 70% alcohol. All procedures were performed under sterile conditions. Midline laparotomy (3 cm) and gentle manipulation of cecum was performed in the sham group. In the sepsis group the cecum was exposed, ligated with silk 2-0, one cm distally to the ileocecal valve to avoid intestinal obstruction. Four punctures were performed with a 22-gauge needle, squeezed gently to force out a small amount of feces, and then it was returned to the abdominal cavity. The abdominal incision was closed with 4-0 nylon sutures. All animals were observed for 24 hours, weighed again and anesthetized with ketamine intramuscular (50 mg/kg). Thorax was opened, blood was collected by cardiac puncture for cytokine assay and leukocyte count.

Experimental design

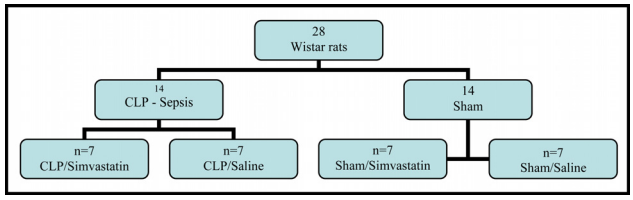

FIGURE 1 - Experimental design: 14 rats were divided into group CLP/sepsis treated with simvastatin (CLP/Simvastatin n=7) and with saline (CLP/saline n=7). In group sham (n=14), rats were treated with simvastatin (Sham/Simvastatin n=7) and with saline (Sham/Saline n=7).

Cytokine assays

Blood samples were used for measurement of tumor necrosis factor-alfa (TNFα), interleukin-1β (IL-1β) and interleukin-6 (IL-6) , determined using enzyme-linked immunoassay kits (all from PeproTech, Rocky Hill, NJ, USA), according to the manufacturer's recommended protocols. The fluorescence was measured by a Bio-Tec Instruments EL 808 ultra microplate reader, using KC4-V3.0 analysis software. Sensitivity of detection was 20 pg/ml for cytokines.

Leukocyte count

Whole blood was collected by cardiac puncture for leukocyte cell counts using a commercially available automated cell counter (Abbott Cell-Dyn 3500R- CD 3500 5L, USA).

Statistical analysis

Data are reported as mean± SEM. Statistical analyses were conducted with commercially available software SPSS 14.0.1 for Windows. Values of p were reported in cases in which

tests were performed. A value of $p<0.05$ was considered significant. ANOVA with post hoc Tukey's test was used to compare the groups.

Results

All the animals survived to experiments. The results were tabulated and exhibited as mean±SD. Leukocyte counts obtained at 24 hours after CLP confirmed significant lowering of WBC and neutrophils in simvastatin treated (CLP/simvastatin) rats of the sepsis group, when compared with the untreated (CLP/saline) rats ($p<0.05$), as can be seen on Table 1. To address possible changes in WBC, neutrophils, limphocytes and eosinophils, secondary to the sham operation, we studied the cells count. No difference was observed comparing the simvastatin (Sham/Simvastatim) treated and saline (Sham/Saline) treated rats ($p>0.05$). To investigate the effects of sepsis and simvastatin treatment on cytokines, serum was isolated from all groups of rats (CLP/saline, CLP-simvastatin, sham/saline, and sham/simvastatin) and subjected to ELISA assay. The levels of TNFα, IL-1β and IL-6 from CLP/simvastatin treated rats were significantly decreased compared with that of CLP/saline rats (Table 2). Cytokines from CLP animals, treated or untreated with simvastatin, displayed an increased levels compared with the sham operated rats ($p>0.05$), as observed in Table 2. No difference was detected among the values of cytokines (pg/mL) from sham rats treated with simvastatin and sham-operated rats treated with saline. ($p>0.05$). This observation indicates that the simvastatin has interference with the expression of cytokines in septic animals, but not in the absence of sepsis.

TABLE 1 - Number of WBC and percent of neutrophils, lymphocytes and eosinophils from the studied rats.

Leukocytes / Groups	*WBC/μL)*(1)*	*Neutrophils (%)*(1)*	*Lymphocytes (%)*(2)*	*Eosinophils(%)*(2)*
CLP/Saline	9,46 ± 1,26ab	76,37 ± 6,57abc	16,36 ± 4,58a	0,39 ± 0,42a
CLP/Simvastatin	6,72 ± 0,39ab	56,50 ± 7,08a	37,03 ± 10,94a	0,57 ± 0,59a
Sham/Saline	4,68 ± 0,56a	57,17 ± 6,60b	34,14 ± 9,26b	5,41 ± 5,16b
Sham/Simvastatin	4,32 ± 0,53b	57,10 ± 8,52c	30,27 ± 8,55b	5,68 ± 5,78b

*Mean ± Standard Deviation; CLP, cecal ligation and puncture.; WBC, white blood cell.
(1) Values followed by the same letter differ among them, considering $p<0.05$ by Tukey test.
(2) Values followed by the same letter do not differ among them, considering $p<0.05$ by Tukey test.

TABLE 2 - Values of TNFα, IL-1β e IL-6 from the studied rats

Groups	TNFα (pg/ml)	IL-1β (pg/ml)	IL-6 (pg/ml)
CLP/Saline	778,5 ± 86[a]	176,9 ± 46[a]	133,6 ± 21[a]
CLP/Simvastatin	364,8 ± 42[a]	66,3 ± 18[a]	58,4 ± 13[a]
Sham/Saline	31,3 ± 6,1	28,1 ± 4	29,8 ± 2
Sham/Sinvastatin	20,7 ± 4,5[a]	27,3 ± 5[a]	23,1 ± 4[a]

*Mean ± Standard Deviation; CLP, cecal ligation and puncture.
(1) Values followed by the same letter differ among them, considering $p<0.05$ by Tukey test.
(2) Values followed by the same letter do not differ among them, considering $p<0.05$ by Tukey test.

Discussion

The 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitor class of drugs (statins) was introduced into clinical practice in the 1980s. They have become the most widely used drugs for lowering plasma cholesterol. Patients with coronary artery disease, highrisk elderly patients, and those having major surgery, benefit from statin therapy[16-19]. Some works have been presenting several effects (anti-inflammatory, antitrombotic, immunomodulator, etc) of the statins, those denominated together as pleiotropic effects, that do not depend on the reductions in the cholesterol levels[20-23,25]. Enlarging the classic use of the statins, the challenge in subject is to evidence other actions of these molecules seen that, many pleiotropic effects have been told, as well as anti-inflammatory properties, action in the endotelial function and benefits in the hemostasia[23-25,]. In the best attempt to understand the anti-inflammatory effects of the simvastatin in the sepsis, rats were previously treated with this drug and submitted to the model of abdominal sepsis by CLP. The levels of pro-inflammatory cytokines and counting of total leukocytes, neutrophils, lymphocytes and eosinphils were analyzed, considering that they are factors that participate actively of the inflammatory process. The experimental model is one of the main means to study sepsis of abdominal origin. The study of the sepsis in experimental models can be driven with administration lipopolissacárides (LPS) intravascular, bacterial peritonitis induced by introduction of feces or bacteria in the peritonial cavity, opening of an intestinal segment or cecal ligation and puncture[26,27]. The CLP model was adopted in this work by presenting some advantages, as it is easy reproducible, simple, it is not necessary the standardization of an inocule. This is the model that better approaches the human sepsis. The sepsis is polymicrobial and simulates the perforated appendicitis or diverticulitis[26]. It is believed that this experimental model is an appropriate study method to evaluate and to control the septic phenomena from its installation to the moment of failure of the organs and systems in different times in this process[28]. The experimental design of this study was elaborated in a such way that the evidences of the anti-inflammatory effect of the sinvastatin in the abdominal sepse were evaluated in currently used biological models. After the

statistical treatment of the results, a discerning analysis of these data resulted in some interesting observations. Except for the groups without infection (group sham), the total leukocytes count indicated an accumulation of these cells as a consequence of the trauma and ischemia on the tissues. The use of simvastatin in the infected rats inhibited the accumulation of the neutrophils, but not in the absence of sepsis. On the other hand, it was observed that in the septic groups, the simvastatin didn't promote significant alteration in the lymphocytes and eosinophils counts. In relation to the cytokines dosages, it was observed that the simvastatin didn't result in a significant change in the levels of TNFα, IL-1β and IL-6 in the sham rats. The abdominal sepsis served to demonstrate a significant anti-inflammatory effect of simvastatin. This fact can be corroborated by the significant reduction of the levels of these cytokines in the infected animals, when simvastatin was administered. These data suggest an important relationship between the statin and the cells of the immune system in the validity of the mechanisms of repair of the traumatic damage, as well as during the activation of the monocytes. Therefore, it was demonstrated in the present work that the serum TNFα, IL-1β, IL-6, total leukocytes and neutrophils had statistically significant reduction ($p < 0,05$) in the groups submitted to the sepsis and treated with simvastatin, compared with those non treated rats. These data corroborate with the work of Villa et al[29], where the levels of TNF-α, IL-1β and IL-6 became altered in the same model of CLP polymicrobial abdominal sepsis. Koo et al[30] demonstrated in CPL model that the expression of genes for these cytokines happen during the abdominal sepse, not only in the intestinal site, but also in other organs. The results obtained in the present work are also in agreement with those visualized by Merx et al[31]. They demonstrated that the simvastatin, injected 20 hours after CLP in the same concentration used in the present study (10 mg/mL), increased the time of survival, as well as it preserved the heart and hemodinamic functions of the studied rats. In this same work it was demonstrated *in vitro* that the monocytes adhesion was increased in the group sepsis, when compared with the group sham. The adhesion decreased when these cells were incubated with simvastatin. The increasing adhesion is an important factor in the physiopathology of the sepsis. The benefit of the anti-inflammatory action of the statins was also analyzed by Merx et al[31,32], who studied the effect of the atrovastatin, pravastatin, simvastatin and fluvastatin in the survival in a CLP model in murines. The authors demonstrated that the treatment after 6 hours of the induction of the sepse increased the time of survival of the animals, except the fluvastatin, that didn't alter the survival. In the present study we did not find difference in survival between the groups, because no mortality occurred. The host reaction to the peritoneal sepsis involves antibodies production, complement activation, cellular immunity and bacterial destruction by polymorphonuclear leukocytes and macrophages[33-35]. The mechanism of the anti-inflammatory action of simvastin is not completely elucidated. However, some hypothesis exist to explain its action. The bacterial toxins are recognized by a variety of receptors in the monocyte surface, macrophages and granulocytes. The cytokines (TNF, IL-1 and IL-6) increase the expression of adhesion molecules (selectines and iCAMs) recruiting neutrófilos for the infection site[35]. The IL-1 produces several effects similar to the exogen TNF, as fever, anorexia and hypotension. It also produces increase in the leukocyte adhesion, bone reabsorption, inhibition of the lipoprotein-lipase and the synthesis of collagen[36]. Great efforts have been used in the attempt of elucidating the action of the statins in the sepsis, because there great therapeutic potential[37,38]. Few clinical studies have been published recently to support the hypothesis of the action of therapy with simvastatin in sepse. Almog et al[39] performed a prospective observacional cohort study to determine the impact of pre-treatment with statins in the occurrence of severe sepse in infected patients. Of the 361 patients with bacterial infection, 82 (23%) had received statins at least 4 weeks before admission. The mortality tax was low and it didn't differ significantly among the 2 groups (3.7% vs 8.6%, P=0.21). Severe sepsis developed in the 2.4% and 19%, of the patients respectively, in the group with statin and without statin. In other retrospective revision of 388 patient with bacteremia, Liappis et al[40] described a significant reduction in the patients' mortality when they received statins in the period of the admission, compared with those without this therapy.

Conclusion

The data of the present study suggest that simvastatin has potential to attenuate or to prevent the effects of the abdominal sepsis in rats subjected to cecal ligation and punture, represented by the reduction of the levels of serum cytokines, total leukocytes and neutrophils.

References

1. Kumana CR, Cheung BM, Lauder IJ. Simvastatin reduced mortality and vascular events in high-risk patients. ACP J Club. 2003; 138:2–3.
2. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004; 350:1495–504.
3. Arnaud C, Mach F. Pleiotropic effects of statins in atherosclerosis: role on endothelial function, inflammation and immunomodulation. Arch Mal Coeur Vaiss. 2005; 98:661–6.
4. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med. 2003; 348:138–50.
5. Riedemann NC, Guo RF, Ward PA. Novel strategies for the treatment of sepsis. Nat Med. 2003; 9:517–24.
6. Bone RC, Fisher CJ Jr, Clemmer TP. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med. 1987; 317:653–8.
7. Annane D. Corticosteroids for septic shock. Crit Care Med. 2001;29:S117–S20.
8. Bernard GR, Vincent JL, Laterre PF. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001; 344:699–709.
9. Fisher CJ, Agosti JM, Opal SM. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. N Engl J Med. 1996; 334:1697–702].
10. Fisher CJ Jr, Slotman GJ, Opal SM. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. The IL-1RA Sepsis Syndrome Study group. Crit Care Med. 1994; 22:12–21.

11. Ziegler EJ, Fisher CJ Jr, Sprung CL. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: a randomized, double-blind, placebo-controlled trial. The HA-1A Sepsis Study Group. N Engl J Med. 1991; 324:429–36.
12. Bernard GR, Wheeler AP, Russel JA, Schein R, Steinberg JP, Fulkerson WJ, Wright PE, Christman BW, Dupont WD, Higgins SB, Swindell BB. The effects of ibuprofen on the physiology and survival of patients with sepsis. N Engl J Med. 1997; 336:912–18.
13. Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nat Med. 2000;6: 1399–402.
14. Pruefer D, Makowski J, Schnell M, Buerke U, Dahm M, Oelert H, Sibekius U, Grandel U, Grimminger F, Seeger W, Meyer J, Darius H, Buerke M. Simvastatin inhibits inflammatory properties of Staphylococcus aureus alpha toxin. Circulation. 2002; 106:2104–10
15. Laufs U, Liao JK. Post-transcriptional regulation of endothelial nitric oxide synthase mRNA stability by Rho GTPase. J Biol Chem. 1998;273:24266–71.
16. Endo A, Kuroda M. Citrinin, an inhibitor of cholesterol synthesis. J Antibiot. 1976; 29: 841-3.
17. Brown AG, Smale TC, King TJ, Hasenkamp R, Thompson RH. Crystal and molecular structure of compactin, a new antifungal metabolite from Penicillium brevicompactum. J Chem Soc. 1976; 1:1165-70.
18. Endo A.The discovery and development of HMG-CoA reductase inhibitors. J of Lipid Res. 1992; 33: 1569-1582.
19. Goldberg AC. Clinical implications of statin event trials. Curr Atheroscler Rep. 2002;4:337-42.
20. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. J Am Med Assoc. 1998; 279:1643-50.
21. Eisenberg DA. Cholesterol lowering in the management of coronary artery disease: the clinical implications of recent trials. Am J Med. 1998; 104(2A):2S-5S.
22. Mach F. Toward a role for statins in immunomodulation. Mol Interv. 2002; 2:478-80.
23. Veillard N, Mach F. Statins: The new aspirin? Cell Mol Life Sci. 2001; 11: 1771–87.
24. Palinski W. Immunomodulation: A new role for statins? Nat Med. 2000; 12:1311–2.
25. Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation. 1998; 97: 1129–35.
26. Garrido AG, Figueiredo LFP, Silva MR. Experimental models of sepsis and septic shock: an overview. Acta Cir Bras. 2004; 19: 82-8.
27. Rodrigues FHOC, Carneiro BGMC, Rocha RF, Petroianu A. Inibição da formação de abscesso abdominal em rato - mortalidade por sepse. Exp Gastroenterol. 2005; 42:50-4.
28. D´acampora AJ, Bernhardt JA, Serafim JDM, Farias DC, Tramonte R. Efeitos da castração pós-natal sobre o tecido pulmonar após sepse experimental de origem abdominal em ratos. Acta Cir Bras. 2004; 19:115-9.
29. Villa P, Sartor G, Angelini M, Sironi M, Conni M, Gnocchi P, Isetta AM, Grau G, Buurman W, van Tits LJ. Pattern of cytokines and pharmacomodulation in sepsis induced by cecal ligation and puncture compared with that induced by endotoxin. Clin Diagn Lab Immunol. 1995; 2:549-53.
30. Koo DJ, Zhou M, Jackman D, Cioffi WG, Bland KI, Chaudry IH, Wang P. Is gut the major source of proinflammatory cytokine release during polymicrobial sepsis? Biochim Biophys Acta. 1999; 1454:289-95.
31. Merx MW, Liehn AE, Janssens U, Lütticken, R, Schrader J, Hanrath P, Weber C. HMG-CoA Reductase Inhibitor Simvastatin Profoundly Improves Survival in a Murine Model of Sepsis. Circulation. 2004; 109:2560-5.
32. Merx MW, Liehn EA, Graf J, van de Sandt A, Schaltenbrand M, Schrader J, Hanrath P, Weber C. Statin treatment after onset of sepsis in a murine model improves survival. Circulation. 2005; 112:117-24.
33. Alkharfy KM, Kellum JA, Frye RF, Matzke GR. Effect of Ceftazidime on Systemic Cytokine Concentrations in Rats. Antimicr Agent Chemother. 2000;44: 3217–9.
34. Chandraa A, Enkhbaatarb P, Nakanob Y, Traberb LD, Traberb DL. Sepsis: Emerging role of nitric oxide nd Selectins. Clinics. 2006; 61:71-6.
35. Almog Y. Statins, Inflammation, and Sepsis. Chest. 2003; 124:740–3.
36. Salles MJC, Sprovieri SRS, Bedrikow R, Pereira AC, Cardenuto SL, Azevedo PRC, Silva TM, Golin V. Síndrome da resposta inflamatória sistêmica/sepse – revisão e estudo da terminologia e fisiopatologia. Rev Ass Med Bras. 1999; 45:86-92.
37. Warnholtz A, Genth-Zotz S, Münzel T. Should Treatment of Sepsis Include Statins.? Circulation. 2005; 111:1735-7.
38. Pleiner J, Schaller G, Mittermaye Fr; Zorn S, Marsik C, Polterauer S, Kapiotis S, Wolzt M. Simvastatin Prevents Vascular Hyporeactivity During Inflammation. Circulation. 2004; 110:3349-54.
39. Almog Y, Shefer A, Novack V, Maimon N, Barski L, Eizinger M, Friger M, Zeller L, Danon A. Prior statin therapy is associated with a decreased rate of severe sepsis. Circulation. 2004; 110:880–5.
40. Liappis AP, Kan VL, Rochester CG, Simon GL. The effect of statins on mortality in patients with bacteremia. Clin Infect Dis.2001; 33:1352–7.

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