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ORIGINAL ARTICLE

Lipid profile and statin use in critical care setting: implications for kidney outcome

Perfil lipídico e uso de estatina em terapia intensiva: implicações no desfecho renal

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ABSTRACT

Objective: To determine whether pre-hospital statin use is associated with lower renal replacement therapy requirement and/or death during intensive care unit stay. **Methods:** Prospective cohort analysis. We analyzed 670 patients consecutively admitted to the intensive care unit of an academic tertiary-care hospital. Patients with ages ranging from 18 to 80 years admitted to the intensive care unit within the last 48 hours were included in the study. **Results:** Mean age was 66±16.1 years old, mean body mass index 26.6±4/9kg/m^2 and mean abdominal circumference was of 97±22cm. The statin group comprised 18.2% of patients and had lower renal replacement therapy requirement and/or mortality (OR: 0.41; 95%CI: 0.18-0.93; p=0.03). The statin group also had lower risk of developing sepsis during intensive care unit stay (OR: 0.42; 95%CI: 0.22-0.77; p=0.006) and had a reduction in hospital length-of-stay (14.7±17.5 days *versus* 22.3±48 days; p=0.006). Statin therapy was associated with a protective role in critical care setting independently of confounding variables, such as gender, age, C-reactive protein, need of mechanical ventilation, use of pressor agents and presence of diabetes and/or coronary disease. **Conclusion:** Statin therapy prior to hospital admission was associated with lower mortality, lower renal replacement therapy requirement and sepsis rates.

Keywords: Hydroxymethylglutaryl-CoA reductase inhibitors; Intensive care units; Renal replacement therapy; Mortality; C-reactive protein

RESUMO

Objetivo: Determinar se o uso pré-admissão hospitalar de estatina está associado com menor necessidade de diálise e/ou óbito durante internação em unidade de terapia intensiva. **Métodos:** Análise de coorte prospectiva. Foram incluídos consecutivamente 670 pacientes admitidos na unidade de terapia intensiva de um hospital acadêmico de cuidados terciários. Os pacientes incluídos deveriam ter entre 18 e 80 anos e ter sido admitidos na unidade de terapia intensiva nas últimas 48 horas. **Resultados:** A média da idade dos pacientes foi de 66±16,1 anos. O índice de massa corporal foi de 26,6±4/9kg/m^2 e a circunferência abdominal média foi de 97±22cm. O grupo que fez uso de estatina pré-admissão hospitalar (18,2% dos pacientes) necessitou menos de terapia de substituição renal e/ou evoluiu para óbito (OR: 0,41; IC95%: 0,18-0,93; p=0,03). O grupo que fez uso de estatina também apresentou menor risco de evoluir com sepse durante a internação na unidade de terapia intensiva (OR: 0,42; IC95%: 0,22-0,77; p=0,006) e teve menor duração da hospitalização (14,7±17,5 dias *versus* 22,3±48 dias; p=0,006). A terapia pré-admissão hospitalar com estatina foi associada a papel protetor no cenário da terapia intensiva independentemente de variáveis confundidoras, como sexo, idade, proteína C-reativa, necessidade de ventilação mecânica, uso de vasopressores e diagnóstico de diabetes e/ou coronariopatia. **Conclusão:** A

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terapia com estatina antes da admissão hospitalar foi associada a menor mortalidade, menor necessidade de terapia de substituição renal e taxa de ocorrência de sepse.

Descritores: Inibidores de hidroximetilglutaril-CoA redutases; Unidades de terapia intensiva; Terapia de substituição renal; Mortalidade; Proteína C-reativa

INTRODUCTION

Similarly to atherosclerosis, during acute and chronic inflammatory processes there are important changes in lipid profile and metabolism. The high density lipoprotein (HDL) cholesterol levels diminish, and the low density lipoprotein (LDL) particles become more susceptible to oxidation, consequently infiltrating more easily on vascular walls. Moreover, increased insulin resistance is observed during systemic inflammation. All these changes are commonly found in critically-ill patients and are recognized as the metabolic syndrome of critical patient.[1-5]

In a chronic scenario, Ridker et al., demonstrated that C-reactive protein (CRP) reduction related to statin therapy was responsible for a lower cardiovascular mortality risk, even in patients with normal lipid profile. These findings were attributed to independent lipid-lowering effects of 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. In fact, clinical studies suggest that many of the benefits observed with statins are related to pleiotropic properties, such as anti-inflammatory effects, antithrombotic action, endothelium activity regulation, antioxidant effects and augmentation of 25-hydroxi-vitamin D, rather than lipid-lowering effect.[6-12]

Observational studies highlighted the potential of statins in the prevention of contrast-induced acute kidney injury (CI-AKI), suggesting that its pleiotropic effects may also exercise nephroprotective actions.[13] These findings were further confirmed in the PRATO-ACS study, a prospective randomized trial, in which Leoncini et al., showed that high-dose rosuvastatin therapy given on patient admission, in an acute scenario, was associated with significant lower rates of renal events, such as CI-AKI, after coronary angiography. However, few studies have seen a direct relation between statin use, mortality and renal replacement therapy (RRT),[14-18] which is the main objective of this study.

OBJECTIVE

To describe the modifications of lipid profile of critically-ill patients and their relation to outcomes in intensive care unit; to analyze the impact of pre-hospital admission statin therapy on renal outcomes and mortality: acute kidney injury, renal replacement therapy requirement and mortality rates.

METHODS

Type of study and subjects

This was a prospective cohort study that considered 670 patients sequentially admitted to the intensive care unit (ICU) of a teaching tertiary care organization. Previous 3HMG-CoA reductase inhibitors therapy was defined by patient record observation upon admission at ICU, since we considered the use of any specific statin during at least previous 6 months.

Patients aged over 18 years and who had ICU admission within the last 48 hours were included in the study. We excluded patients not to be considered for resuscitation, who underwent kidney transplantation, on chronic dialysis program, and who had already received RRT.

Laboratory analysis

A volume of 30mL of blood in ethylene diamine tetra-acetic acid (EDTA) anti-coagulant was collected from each individual for renal function analysis (blood urea nitrogen and creatinine; Labtest®, Lagoa Santa, MG, Brazil and the Jaffe modified method, respectively), lipid profile (HDL and LDL cholesterol; automated method equipment, Cell-Dyn Ruby; Abbott Diagnostics, Lake Forest, IL, USA), markers of systemic inflammatory response syndrome, CRP, albumin (Immunlite 1,000 immunoassay system, Erlangen, Germany), and the colorimetric method in automated equipment.

Charts were reviewed for clinical and epidemiological data and patients were allocated into Group Statin if they had prior statin use at least for the previous 6 months. Patients without prior statin use were allocated into Non-Statin Group.

Acute kidney injury and sepsis definition

Acute kidney injury (AKI) was defined according to Acute Kidney Injury Network (AKIN) criteria.[16] It was considered as AKI any decrease of renal function in the last 48 hours, characterized by an increase in absolute serum creatinine (sCr) of at least 26.5μmol/L (0.3mg/dL), an increase in sCr $\geq$50% (1.5-fold baseline value, or a decrease in the urine output (UO) <0.5mL/kg/hour for more than 6 hours.

Acute renal injury stage 1 corresponds to the risk class, but it also considers an absolute increase in SCr

≥26.5μmol/L (0.3mg/dL). Stages 2 and 3 correspond to injury and failure classes, respectively. Stage 3 also includes all patients requiring RRT. Sepsis was defined based on the Surviving Sepsis Campaign Guidelines Committee.[19]

Primary endpoints

Our primary endpoints were occurrence of AKI, requirement of RRT and mortality.

Secondary endpoints

Our secondary endpoints were the occurrence of sepsis and determination of lipid profile of enrolled patients.

Statistical analysis

Data were analyzed using the software Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, Inc., Chicago, IL, USA). Numerical data were presented as mean and standard deviation (SD) or as median and range. Categorical variables were expressed as total number and percentage.

Comparisons between groups were performed using Student *t* test for parametric variables. Non-parametric variables were compared using one-way analysis of variance (ANOVA) test, followed by Bonferroni as a posttest.

Binary logistic regression analysis was used to study variables associated with sepsis and RRT and/or death. All results were considered significant at $p<0.05$. Groups were adjusted to age, sex, CRP levels, need of mechanical ventilation, use of vasopressors and presence of diabetes and coronary arterial disease.

Receiver Operating Characteristic (ROC) curve was used to demonstrate the accuracy of HDL-cholesterol dosage test in determining the risk of RRT need and/or mortality.

This study was carried out in compliance with ethical standards determined by resolution 466/12 of *Conselho Nacional de Saúde*, and approved by the Research Ethics Committee, opinion no. 1.290.566, CAAE: 23420414.9.0000.5505.

RESULTS

Demographic variables

Of the sample, 64% of patients were male. The mean age of patients included in this study was 66±16.1 years. They had a mean body mass index (BMI) of 26.6±4.9kg/m^2 and a mean abdominal circumference of 97±22cm (Table 1). Regarding the use of statins, 67 (54.5%) of the patients used atorvastatin, 43 (35.5%) simvastatin, 11 (9.1%) rosuvastatin and 1 (0.9%) used pravastatin.

Table 1. Baseline characteristics of patients admitted to the intensive care unit stratified by the use or not of statins

Parameters	Total (n=670)	Pre-hospital statin use (n=122)	No use of statin (n=548)	p value
Age, years	431 (64.3)	89 (73)	343 (62.6)	0.010
BMI, kg/m^2	66.0±16.1	69.4±12.4	65.2±16.8	0.002
Abdominal circumference, cm	26.6±4.9	27.2±4.6	26.5±5.0	0.166
APACHE II score	97.0±22.0	96.7±24.1	97.7±20.3	0.740
Creatinine, mg/dL	18.0±6.26	17.1±5.3	18.3±6.3	0.040
eGFR, mL/min/1.73m^2	1.1±0.89	1.0±0.45	1.2±0.96	0.003
CRP, mg/dL	73.05±16.2	76.5±18.3	69.6±14.1	0.070
Cholesterol (total), mg/dL	8.5±12.9	6.1±7.1	8.7±12.3	0.002
HDL-cholesterol, mg/dL	123.0±52.6	132.0±54.0	121.3±51.8	0.040
LDL-cholesterol, mg/dL	31.9±16.2	34.7±11.7	31.3±17.0	0.008
Triglycerides, mg/dL	69.6±40.6	70.3±45.0	69.3±39.4	0.792
Mechanical ventilation at admission to ICU	110.0±72.3	125.6±97.8	106.9±64.7	0.040
Diabetes mellitus	83.7 (12.5)	14 (12.3)	69 (12.6)	0.283
Coronary artery disease	126 (19.1)	34 (27.9)	94 (17.2)	0.007
Nephrotoxic drugs	110 (16.7)	40 (32.8)	72 (13.2)	<0.001
Antimicrobials	432 (65.0)	83 (68.0)	350 (64.0)	0.320
Iodinated contrast	228 (34.0)	46 (38.0)	175 (32.0)	0.090
Non-steroidal anti-inflammatory drugs	146 (22.0)	26 (21.0)	132 (24.0)	0.480
Anti-inflamatórios não esteroidais	58 (8.6)	11 (9.0)	43 (8.0)	0.630

Results expressed as n (%), or mean±standard deviation.
BMI: body mass index; APACHE: Acute Physiology and Chronic Health Evaluation; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ICU: intensive care unit.

Diagnosis at admission in intensive care unit

The most common reason for ICU admission was sepsis due to respiratory infection, accounting for 34.7% of cases. Gastrointestinal/hepatic diseases accounted for 12.6%, and cardiovascular diseases for 7.9% of cases. Causes of admission to ICU are summarized in table 2.

Table 2. Main cause for intensive care unit admission of critically-ill patients

Main cause for ICU admission	Total (n=670)	Pre-hospital statin use (n=122)	No use of statin (n=548)	p value
Cardiovascular	53 (7.9)	5 (4.3)	20 (3.6)	0.74
Respiratory	10 (1.4)	1 (0.6)	4 (0.8)	0.81
Gastrointestinal/hepatic	85 (12.6)	5 (4.5)	44 (8.1)	0.01
Metabolic	10 (1.4)	1 (0.5)	5 (0.9)	0.71
Trauma	10 (1.4)	1(0.7)	3 (0.7)	0.98
Surgical	42 (6.2)	4 (3.4)	15 (2.8)	0.83
Sepsis	454 (67.5)	206 (30.6)	258 (38.5)	0.07
Respiratory	233 (34.7)	104 (15.5)	128 (19.2)	0.63
Abdominal	95 (14.1)	35 (5.2)	60 (8.9)	0.08
Gastrointestinal	31 (4.6)	13 (2.0)	18 (2.6)	0.75
Urinary	21 (3.1)	7 (1.1)	14 (2.0)	0.02
Without focus definition	74 (11)	35 (6.8)	39 (5.8)	0.69

Results expressed as n (%).
ICU: intensive care unit.

Table 3. Outcomes of patients admitted to the intensive care unit stratified by the use or not of statins

Parameters	Total (n=670)	Pre-hospital statin use (n=122)	No use of statin (n=548)	p value
Hospital stay, days	21.0±44.3	14.7±20.5	22.3±48	0.006
ICU stay, days	4.6±9.5	4.7±17.5	4.5±6.5	0.828
Days free of AKI	4.1±33.0	10.0±56.0	2.8±25.2	0.030
Use of vasopressors at ICU	56 (8.4)	9 (7.4)	47 (8.6)	0.683
Dialysis requirement	61 (9.1)	11 (9.0)	5 (9.2)	0.062
Sepsis	157 (23.4)	15 (12.3)	140 (25.7)	0.001
Mortality	49 (7.3)	5 (4.1)	44 (8.0)	0.089
Duration of acute kidney injury, days	5.3±4.6	3.7±4.0	6.8±5.3	0.020

Results expressed as mean±standard deviation.
ICU: intensive care unit; AKI: acute kidney injury.

Table 4. Stratification of plasma levels of cholesterol particles within three groups of patients: without acute kidney injury, with acute kidney injury but not dialysis need and patients who needed dialysis or died

	Control Group (n=580)	Patients with AKI but no renal replacement therapy (n=40)	Renal replacement therapy or death (n=36)	p value
Cholesterol (total), mg/dL	126.5±50.9	131.3±48.1	81.7±48.4*	<0.05
HDL-cholesterol, mg/dL	33.3±15.9	34.6±14.5	18.7±14.8*	<0.05
LDL-cholesterol, mg/dL	71.6±39.6	74.0±39.2	45.5±38.2*	<0.05
Triglycerides, mg/dL	108.7±72.6	111.5±67.2	114.6±82.2	NS

* p<0.05: renal replacement therapy or death *versus* Control Group and renal replacement therapy *versus* patients with acute kidney injury but no renal replacement therapy.
AKI: acute kidney injury; HDL: high density lipoprotein; LDL: low density lipoprotein; NS: non-significant.

Outcomes

Approximately 18% of patients (122) were on statin therapy prior hospitalization for at least 6 months. Patients who were on statin therapy prior to admission had a lower CRP level compared to those who were not on HMG reductase inhibitors (6.1±7.1mg/dL *versus* 8.7±12.3mg/dL; p=0.002). Statin Group also had higher levels of HDL-cholesterol (34.7±11.7mg/dL *versus* 31.3±17mg/dL; p=0.008), shorter hospital-stay (14.7±20.5 days *versus* 22.3±48 days), and more days free of AKI than the Control Group (10.0±56 days *versus* 2.8±25.2 days; Table 3).

The group that required RRT (n=91) and/or died had a lower percentage of patients using statin before hospital admission than Control Group (9.0% *versus* 19.6%; p<0.008), and had higher levels of CRP than the Control Group (14.8±22.8mg/dL *versus* 7.6±10.3mg/dL; p<0.001) at ICU admission (data not shown). Patients who required RRT or died had statistically significant lower HDL-cholesterol levels (p<0.05) (Table 4).

Pre-admission statin therapy demonstrated a protective role in our cohort of critically ill patients, resulting in an improvement of both kidney and patient outcome combined. Patients using statin prior to hospital admission were less likely to require RRT and/or die (OR: 0.4; 95%CI: 0.1-0.86; p=0.01) (Table 5). Such relation remained significant even when controlled for major confounders (sex, age, CRP levels, need for mechanical ventilation or vasopressors during ICU stay, presence of diabetes and coronary disease at ICU admission) in multiple binary logistic regression analysis (OR: 0.41; 95%CI: 0.18-0.93; p=0.03) (Table 5).

Moreover, patients on statin therapy prior to hospitalization were less likely to develop sepsis (OR: 0.4; 95%CI: 0.22-0.71; p=0.02) during their stay at ICU. When controlled for major confounders (sex, age, CRP levels, mechanical ventilation or vasopressors use at ICU, diabetes, coronary disease and eGFR) the relation was still significant (OR: 0.44; 95%CI: 0.22-0.93; p=0.03).

Table 5. Association of pre-hospital use of statins and need of dialysis therapy or death during intensive care unit stay

Renal replacement therapy and/or death	OR	95%CI	p value
Unadjusted	0.40	0.19-0.86	0.01
Adjusted for sex	0.41	0.19-0.87	0.02
Adjusted for sex and age	0.41	0.19-0.89	0.02
Adjusted for sex, age and CRP	0.45	0.21-0.97	0.04
Adjusted for sex, age, CRP and mechanical ventilation at ICU	0.41	0.18-0.92	0.03
Adjusted for sex, age, CRP, mechanical ventilation and use of vasopressors at ICU	0.40	0.17-0.90	0.02
Adjusted for sex, age, CRP, mechanical ventilation, use of vasopressors at ICU and diabetes	0.41	0.18-0.93	0.03
Adjusted for sex, age, CRP, mechanical ventilation, use of vasopressors at ICU, diabetes and coronary artery disease	0.41	0.18-0.93	0.03
Adjusted for sex, age, CRP, mechanical ventilation, use of vasopressors at ICU, diabetes, coronary artery disease and eGFR	0.44	0.22-0.93	0.03

OR: odds ratio; 95%CI: 95% confidence interval; CRP: C-reactive protein; ICU: intensive care unit; eGFR: estimated glomerular filtration rate.

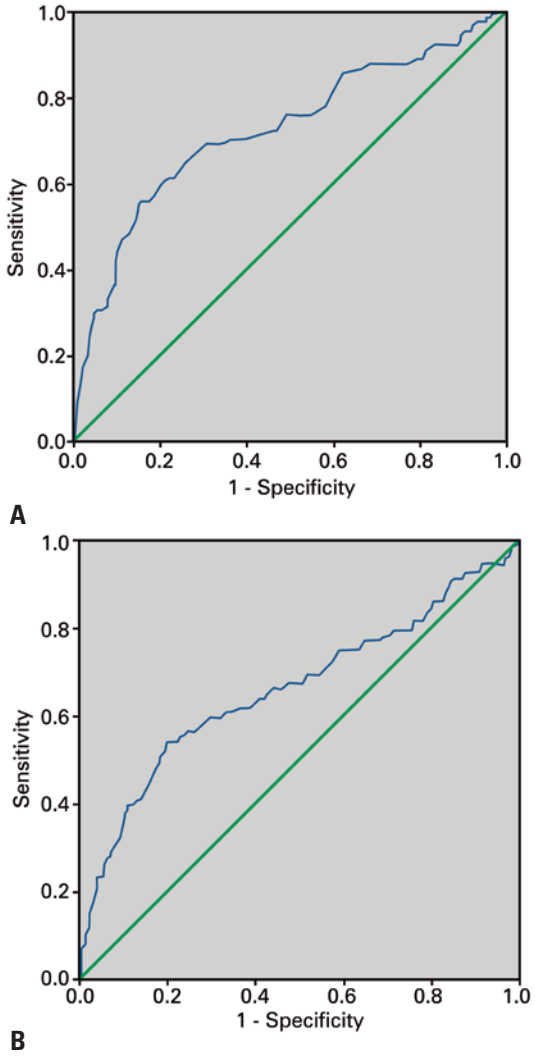

Figure 1. ROC curves demonstrating relation between high-density lipoprotein levels and outcomes (A) and low-density lipoprotein levels and outcomes (B)

The relation between low HDL-cholesterol levels and the combined outcome (RRT need and/or death) was demonstrated on ROC curve with the area under the curve of 0.727 for HDL ($p<0.05$). This relation was not present between LDL-cholesterol levels and the studied outcome (Figure 1). The area under the curve demonstrates that lower high-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels were associated with higher incidence of RRT need and/or death.

DISCUSSION

The efficacy of statins in modifying cardiovascular risks is well established, even in patients with a normal lipid profile, which demonstrates the importance of the pleiotropic effects of this class of drugs. In our study, the pre-hospital statin use was associated with the attenuation on kidney dysfunction and sepsis outcomes in critical care setting. There are many similarities in the pathogenesis of atherosclerosis, sepsis and AKI, including inflammation and endothelial dysfunction. Regulation of any of these pathways may explain the beneficial effects of statins use in critical care.[6]

It is known that critically ill patients develop metabolic changes, such as insulin resistance, disruption of cortisol metabolism and lipid profile, due to systemic inflammation. These metabolic modifications are similar to those seen in traditional metabolic syndrome and are noticed in both acute and recovery phase of systemic inflammation.[17]

Lower HDL-cholesterol levels are markers of poor prognosis in critical care patients. In our study, a relation between HDL-cholesterol levels and patient outcome during ICU stay was clearly demonstrated, which is in agreement with the metabolic syndrome of critically ill patient hypothesis. These markers are associated with greater need of RRT incidence and higher mortality. We also found that those patients who developed AKI and required RRT had lower levels of HDL-cholesterol at ICU admission, and the magnitude of the observed reduction was also related with worse prognosis. Early reports have already characterized the metabolic syndrome of critical patients as hypertriglyceridemia and lower levels of HDL-cholesterol. Furthermore, it has also been suggested, in those previous studies, that the magnitude of change in lipid profile during systemic inflammation is proportional to the severity of inflammatory response and is related to patient's prognosis.[17,18]

Murch et al., reviewed the pathophysiology of metabolic syndrome of critical patient, and demonstrated

that lipoproteins neutralize lipopolysaccharides and exert direct anti-inflammatory actions, suggesting that HDL and LDL particles are important regulators of human immune response to endotoxemia.[19] In addition, Wendel et al., had already shown that serum triglyceride levels frequently increase in systemic inflammatory conditions, such as sepsis, due to reduced triglyceride hydrolysis and fat oxidation, determining inflammation-insulin resistance and amplifying inflammation cascade.[20]

Additionally, we demonstrated that a pre-admission use of statins was associated with lower rate of RRT requirement and/or mortality. During ICU stay, AKI is a well-known risk factor for death, particularly when RRT is required. Acute kidney injury in critical patients is usually due to many factors, such as dehydration, nephrotoxicity, inflammation and micro-thrombosis. Many mechanisms could explain the beneficial effect of statins in this scenario. Our group had already demonstrated the reversion of inflammatory imbalance at cell level, achieved with statin therapy. In that study, the treatment of peripheral mononuclear cells exposed to lipopolysaccharides of critically ill patients with simvastatin led to a decrease in interleukin 10 and tumor necrosis factor alpha (TNF-α) production, highlighting the immunomodulatory potential of such agents.

Statins are known to modulate endothelial function by promoting the synthesis of nitric oxide synthase enzyme, culminating in vasodilator effect and less oxidative injury. Studies with animal models suggest that statins have an inhibitory effect on leucocyte adhesion and transendothelial neutrophil migration, modulating the inflammatory response.[11]

In acute scenarios, observational studies have already shown that HMG-CoA reductase inhibitors therapy is associated with lower incidence of CI-AKI after coronary angiography and percutaneous coronary intervention. The PRATO-ACS study has also demonstrated a relation of statin therapy on admission with better renal outcomes and lower CI-AKI incidence.[14] Statins are able to reduce protein endocytosis in the proximal tubule, resulting in less inflammation and tubular damage. Multiple mechanisms are involved in CI-AKI, but it is known that inflammation plays an important role. That is why the effect of statin therapy on reducing inflammatory cascade can be responsible for nephroprotective action of this class of drug. Likewise, pre-admission use of statin in critically ill patients may lead to better renal outcomes during ICU stay.

In agreement to our data, Singh et al., in their meta-analysis study, have shown a 33% reduction in the risk of RRT in the group of patients who received preoperative statin therapy before undergoing coronary artery bypass graft.[13] It has already been demonstrated that preoperative statin therapy was associated with a reduction in postoperative myocardial infarction, stroke and atrial fibrillation. On the other hand, Prowle et al., in a double-blinded, randomized controlled trial, failed to detect a protective effect of perioperative statin therapy on AKI after cardiac surgery with cardiopulmonary bypass.[21]

In our study, as a secondary endpoint, we found that pre-hospital use of statins was associated with lower rate of sepsis during ICU stay, since this class of drug can modulate the inflammatory response in its initial phases, when organ dysfunction is not yet established. Our group had already shown that peripheral blood mononuclear cells isolated from critically ill patients with AKI when treated with simvastatin had lower TNF-α production than that of healthy Control Group. Currently available evidence suggests, as seen in our study, that the pleiotropic effects of statin could be beneficial during sepsis. In fact, Feng et al., demonstrated that in patients with sepsis using rosuvastatin as the reference, atorvastatin and simvastatin had superior efficacy in preventing mortality.[22-30] Additionally, Craig et al., reported in their randomized, double-blinded, placebo-controlled trial, that some components of Sequential Organ Failure Assessment (SOFA) score, such as coagulation, renal and cardiovascular components, were improved at day 14 in simvastatin group. This improvement in organ dysfunction is considered to be related to the effect of statin on preservation of endothelial function.[31]

Limitations

The present study demonstrated evidence of a beneficial role of using statins in critical care patients. Our results were generated, primarily, based on a prospective analysis, but some confounders could not have been measured. It also has a small sample of patients, which may contribute to statistical limitations. The heterogeneity of type and dosage of statin used by patients in our study may also lead to difficulties in analysis. It was also a single-center study, restricted primordially to patients with clinical pathologies.

Large-scale prospective clinical trials are needed to deepen our knowledge in this field. Moreover, it is still not clearly known the extent and kind of side effects of statins in critically ill patients.

CONCLUSION

Critically ill patients present peculiar lipid profile modifications that are closely related to the magnitude of inflammatory response, leading to what is called metabolic syndrome of intensive care unit. Statin therapy prior to hospital admission was associated with better outcomes during intensive care unit stay, such as lower risk for renal replacement therapy requirement and/or mortality, probably attributed to its pleiotropic effects on inflammation, endothelial regulation, and oxidative stress damage.

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AUTHORS' CONTRIBUTIONS

IM and MCB designed research; IM and BMQ conducted research; BMQ, MSDJR, JCMM and OFPS, provided essential materials; IM, MCB and BMQ, analyzed data or performed statistical analysis; IM, wrote paper; IM and MCB, had primary responsibility for final content. All authors read and approved the final manuscript.

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