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The incidence of delirium in patients pretreated with statins who remain in an intensive care unit after cardiac surgery

Incidência de delirium durante a internação em unidade de terapia intensiva em pacientes pré-tratados com estatinas no pós-operatório de cirurgia cardíaca

ABSTRACT

Objective: To determine the association between the preoperative administration of statins and postoperative delirium in a prospective cohort of patients undergoing cardiac surgery.

Methods: All adult patients who were admitted to the intensive care unit following cardiac surgery between January and June 2011 were included. Delirium was screened during the postoperative period using the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC).

Results: A total of 169 patients underwent elective cardiac surgery, and 40.2% of the patients were treated preoperatively with statins. Delirium was identified using the CAM-ICU in 14.9% of patients not taking preoperative statins in comparison with 11.8% of the patients taking statins (p = 0.817). Using the ICDSC, delirium was identified in 18.8% of patients not taking statins in comparison with 10.3% of the patients taking statins (p = 0.191).

Conclusion: The use of preoperative statins is not correlated with postoperative delirium in patients undergoing cardiac surgery.

Keywords: Cardiac surgery/drug effects; Delirium/etiology; Hydroxymethylglutaryl-CoA reductase inhibitors/adverse effects; Postoperative period; Intensive care units

INTRODUCTION

Delirium is an acute onset transient mental condition that is characterized by reduced cognition and consciousness levels, inattention, increased or reduced psychomotor activity and sleep-wake cycle disturbances.[1] Several mechanisms have been proposed for the pathophysiology of delirium, including inflammation and provide a rationale for the use of anti-inflammatory drugs in this context.[2,3,4]

Studies have suggested that preoperative statin treatment may increase the incidence of postoperative delirium, therefore, increasing morbidity and mortality rates compared with other drugs that do not influence the self-regulation of blood microcirculation in the elderly.[5] However, another study has shown protective statin effects, which would reduce the postoperative incidence of delirium.[6] The administration of statins reduced the risk of delirium in 46% of the patients. In addition, two other studies have shown that statins did not change the clinical presentation of delirium after cardiac surgery.[7,8] The anti-thrombotic, anti-inflammatory and immunomodulatory actions of statins are likely to be responsible for their protective effects.[9-11]

Study conducted at Intensive Care Unit, Hospital São José - Criciúma (SC), Brazil.

Conflicts of interest: None.

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Therefore, this study aimed to determine if there is an association between preoperative statin administration and delirium in patients undergoing cardiac surgery in the Hospital São José de Criciúma in Santa Catarina, Brazil.

METHODS

This observational, prospective, cohort study was approved by the ethics committee of the Hospital São José de Criciúma in Santa Catarina, Brazil. Those patients older than 18 years of age who were admitted to the intensive care unit (ICU) following cardiac surgery between January and June 2011 were included. The patients were followed pre- and post-operatively until their hospital discharge and were categorized as patients taking a statin drug (statin group) and patients not taking statin drugs (no statin group) as prescribed by each patient's treating physician.

The data were collected from the medical charts and interviews either with patients staying in the ICU or their family members. The included patients were screened for delirium twice daily until discharge from the ICU by three of the authors, who were previously trained on two different diagnostic scores, i.e., CAM-ICU (Confusion Assessment Method for Intensive Care Unit) and ICDSC (Intensive Care Delirium Screening Checklist). The CAM-ICU diagnostic criteria include four items: 1) acute onset or fluctuating course; 2) inattention; 3) disorganized thinking; and 4) an altered level of consciousness. The delirium diagnosis using the CAM-ICU requires that items 1, 2 and 3 and/or 4 are present.[12] The ICDS diagnostic criteria[13] include altered level of consciousness, inattention, disorientation, hallucination, psychomotor agitation or retardation, inappropriate speech, sleep-wake cycle disturbances and overall symptom fluctuation. Scores that are higher than 4 indicate clinical delirium, whereas scores that are between 1 and 3 indicate subclinical delirium.

To better analyze the influence of statins on the incidence of delirium, we assessed the presence of risk factors, such as preoperative factors (age, gender, a history of stroke, peripheral vascular disease, depression, renal disease, diabetes mellitus, hypertension, acute myocardial infarction, arrhythmia, heart failure and anemia) and intraoperative factors (valve replacement, myocardial revascularization or both). The statins were assessed according to the type of statin and dose.

For statistical analysis, SPSS 17.0 statistical software was used. Additionally, 95% confidence intervals were calculated, and a significance level of $\alpha = 0.05$ was adopted. The quantitative intergroup (statin versus no statin groups) variables were compared using the Student's t test. The qualitative variables were compared using a Chi-squared test. A hazard ratio was used to correlate the preoperative use of statins with the incidence of delirium.

RESULTS

During the study period, 169 patients were assessed, of whom 68 (40.2%) used statins and 101 (59.8%) did not. Out of the 68 patients, 63 (92.6%) used simvastatin and 4 (5.9%) used atorvastatin. Only one patient (1.5%) used rosuvastatin. The exact time of drug intake before surgery could not be determined because the patients could not provide accurate information. However, in all cases, statins were taken for at least two months.

Table 1 shows the clinical and demographic characteristics for all of the study patients classified by their use of statin drugs. No significant difference was found for the variables assessed. As shown in Table 2, the surgery profile was not significantly different between the groups. Regarding the prognostic scores, the Sequential Organ Failure Assessment (SOFA) as measured on the first ICU day was higher among those patients not taking statins ($p = 0.024$), particularly due to the cardiovascular score.

Regarding the postoperative information (Table 3), the mean use of vasoactive drugs (days) was higher in the no statin group ($p = 0.022$); the mean norepinephrine dose was significantly higher in this group ($p = 0.013$). Few patients were sedated (n = 10); of these sedated patients, 70% used benzodiazepines. In addition, few patients used corticoids (n = 3) and anti-cholinergic drugs (n = 1).

All other parameters compared were similar for both groups. The median (25-75) time (days) to develop delirium was 2 (1-3) for both CAM-ICU and ICDSC assessments. There was no intergroup difference in either the incidence of delirium as assessed with ICDSC and CAM-ICU or subclinical delirium as assessed with ICDSC (Table 3). The median (25-75) days with delirium were 2 (1-3) measured utilizing both assessment methods with no significant intergroup difference. In addition, the mean time for developing delirium was similar for all study patients regardless of their use of a statin drug (data not shown). The median time (25-75) of the ICU stay was 2 (2-3) for both groups. The hospital mortality rate was 4.7%.

Table 1 - Population characteristics stratified by the preoperative use of statins

Variable	Statin		p value
	No N (%) N = 101	Yes N (%) N = 68	
Age, mean (±SD)	61.51 (±11.4)	62.85 (±10.9)	0.448
Gender N (%)			0.146
Female	41 (40.6)	20 (29.4)	
Male	60 (59.4)	48 (70.6)	
Arterial hypertension, N (%)			0.826
No	15 (14.9)	9 (13.2)	
Yes	86 (85.1)	59 (86.8)	
Diabetes Mellitus, N (%)			1
No	67 (66.3)	46 (67.6)	
Yes	34 (33.7)	22 (32.4)	
Angina, N (%)			0.25
No	70 (69.3)	41 (60.3)	
Yes	31 (30.7)	27 (39.7)	
NYHA II/III, N (%)			1
No	83 (82.2)	56 (82.4)	
Yes	18 (17.8)	12 (17.6)	
NYHA IV, N (%)			0.649
No	98 (97.0)	67 (98.5)	
Yes	3 (3.0)	1 (1.5)	
Previous AMI, N (%)			0.165
No	77 (76.2)	45 (66.2)	
Yes	24 (23.8)	23 (33.8)	

NYHA – New York Heart Association; AMI – acute myocardial infarction. The data are shown as the mean ± standard deviation (SD) or the median.

Table 2 - Surgery profile stratified by the preoperative use of statins

Variable	Statin		p value
	No N = 101	Yes N= 68	
Type of admission (days)			0.455
Urgency/Emergency	25 (24.8)	13 (19.1)	
Elective	76 (75.2)	55 (80.9)	
Procedure			0.132
MRS	71 (70.3)	60 (88.2)	
Valve replacement	23 (22.8)	6 (8.8)	
MRS	1 (1.0)	0 (0.0)	
MRS + valve replacement	2 (2.0)	2 (2.9)	
Correction of IAD	2 (2.0)	0 (0.0)	
Correction of aneurism	1 (1.0)	0 (0.0)	
Aortic dissection	1 (1.0)	0 (0.0)	
ECC			0.305
No	34 (33.7)	17 (25.0)	
Yes	67 (66.3)	51 (75.0)	
ECC time (minutes)	53.6 ± 47.3	58.0 ± 39.8	0.533
Ischemic time (minutes)	34.9 (±30.6)	38.2 (±28.7)	0.488
APACHE II	13.1 (±5.27)	13.5 (±4.58)	0.61
SOFA D1	4.57 (±3.18)	3.51 (±2.58)	0.024*
SOFA D3	3.35 (±2.54)	2.55 (±1.9)	0.075

MRS - myocardial revascularization surgery; IAD - interatrial defect; ECC - extracorporeal circulation; APACHE - Acute Physiology and Chronic Health Evaluation; SOFA - Sequential Organ Failure Assessment. The data are shown as the number (percentage) or the mean ± standard deviation.

Table 3 - Postoperative profile stratified by the preoperative use of statins

Variable	Statin		p value
	No N = 101	Yes N = 68	
MV > 24 hours			1
No	93 (92.1)	63 (92.6)	
Yes	8 (7.9)	5 (7.4)	
Vasoactive drugs > 24 hours			0.078
No	69 (68.3)	55 (80.9)	
Yes	32 (31.7)	13 (19.1)	
Days on vasoactive drugs	1.33 (±2.5)	0.66 (±1.1)	0.022*
Norepinephrine dose	6.75 (±15.6)	3.75 (±7.0)	0.013*
Blood transfusion			0.852
No	79 (78.2)	52 (76.5)	
Yes	22 (21.8)	16 (23.5)	
Delirium ICDSC			0.191
No	82 (81.2)	61 (89.7)	
Yes	19 (18.8)	7 (10.3)	
Subclinical delirium ICDSC			0.752
No	40 (49.6)	29 (42.6)	
Yes	61 (60.4)	39 (57.4)	
Delirium CAM-ICU			0.817
No	86 (85.1)	60 (88.2)	
Yes	15 (14.9)	8 (11.8)	

MV – mechanical ventilation; ICDSC – Intensive Care Delirium Screening Checklist; CAM-ICU – Confusion Assessment Method for Intensive Care Unit. The data are shown as the number (percentage) or the mean ± standard deviation.

DISCUSSION

In this observational, prospective study, no statin protective effect against postoperative delirium was identified. The incidence of delirium in this study population was 15.4% as assessed with ICDSC and 13.6% with CAM-ICU, which corresponds to 26 and 24 patients, respectively. This finding is similar to that reported in the medical literature. Rudolph[14] describes delirium as a frequent complication after cardiac surgery with incidences that range between 3 and 50%. This wide range of incidences is explained by Ouimet[15] derived from the discrepancies between the patients studied, interpretation of clinical signs and diagnostic screening.

The most frequent surgical procedure was myocardial revascularization, 77.5%. The use of this procedure had no influence on the results because the frequency was similar for both groups. The procedure most related with delirium is either valve replacement or the association of valve replacement and myocardial revascularization.[16] In our study, these procedures were conducted in 17.2% and 2.4% of the patients. The extracorporeal circulation time and the time of ischemia, both related with surgery complexity and an increased incidence of delirium, were similar for both groups.

Although the surgical profile was similar for both groups, the patient group who did not receive statins had a higher SOFA score as measured on the first day in ICU, which is associated with the higher use of vasoactive drugs and higher mean norepinephrine doses; therefore, the no statin group had worse immediate postoperative courses. However, on the third postoperative day, both groups were similar and had no significant difference for the other assessed parameters.

Simvastatin was used by 92.6% of the patients. Simvastatin has lipophilic properties that allow the drug to cross cell membranes and the blood-brain barrier.[17] Lovastatin is lipophilic. However, lovastatin has a higher blood-brain barrier permeability compared with simvastatin. The study conducted by Saheki[17] also demonstrates that pravastatin, which is lipophobic, does not cross the blood-brain barrier. As the range of statins used by patients in this study was narrow, the eventual influence of different types of statins on the incidence

of delirium could not be assessed. Perhaps statins with increased penetration into the central nervous system (CNS), such as lovastatin, have a different incidence of delirium. Several studies have assessed the statins' systemic effects, pleiotropic effects, which can differ between different drugs; this difference could indirectly influence neurological findings.

The duration of statin use could not be accurately assessed. Botti[18] has demonstrated that short-term statin therapy had no influence on brain cholesterol levels. These results may be an explanation for the lack of statin protective effects against delirium. Treatments longer than six months reduce the levels of cerebrospinal fluid cholesterol.[19] Zacco[20] has demonstrated that statins activate neuroprotective pathways, as cortical neurons exhibited a cholesterol-dependent resistance to excitotoxicity, which was reversible after administering mevalonate and cholesterol.

The interpretation of these data should consider the study limitations. First, single-center study had a limited number of patients. Therefore, peculiarities of this center may have influenced the results. In addition, it was calculated *a posteriori* that given the observed proportions (14.9 versus 11.8), a sample of 1,890 patients in each group would be required to measure a significant intergroup difference for the incidences of delirium with an alpha of 0.05 and 80% power. Second, the vast majority of surgical interventions were related to myocardial revascularization, frequently with no extracorporeal circulation, i.e., a group of patients less prone to develop delirium. In addition, different statins were analyzed together, which may have a confounding effect considering the pharmacokinetics and pharmacodynamics of different statins.

CONCLUSION

No correlation was found between preoperative administration of statins and the incidence of delirium in patients undergoing cardiac surgery.

RESUMO

Objetivo: Determinar a associação entre a administração pré-operatória de estatina e o delírium pós-operatório em uma corte prospectiva de pacientes submetidos à cirurgia cardíaca.

Métodos: Foram analisados pacientes adultos internados na unidade de terapia intensiva após cirurgia cardíaca entre janeiro e junho de 2011. A triagem para *delirium* foi realizada utilizando o *Confusion Assessment Method* para analisar *delirium* em uma unidade de terapia intensiva (CAM-ICU) e *Delirium Screening Checklist* para terapia intensiva (ICDSC) durante a internação na terapia intensiva

Resultados: Cento e sessenta e nove pacientes foram submetidos à cirurgia cardíaca eletiva, dos quais 40,2% estavam utilizando estatina no pré-operatório. *Delirium* foi identificado em 14,9% dos pacientes que não utilizavam estatina comparado com 11,8% dos que utilizavam (p=0,817) quando avaliados pelo CAM-ICU. Utilizando o ICDSC 18,8% dos pacientes que não usam estatina comparado com 10.3% dos que usam (p=0,191).

Conclusão: Não há relação entre uso de estatinas com a ocorrência de *delirium* em pacientes submetidos a cirurgia cardíaca.

Descritores: Cirurgia cardíaca/efeitos de drogas; Delírio/etiologia; Inibidores de Hidroximetilglutaril-CoA redutases / efeitos adversos; Período pós-operatório; Unidades de terapia intensiva

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