

Outcomes from intracerebral hemorrhage among patients pre-treated with statins

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ABSTRACT

Objective: 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have been associated with improved clinical outcomes after ischemic stroke and subarachnoid hemorrhage, but with an increased risk of incidental spontaneous intracerebral hemorrhage (ICH). We investigated whether the statin use before ICH, was associated with functional independence, 90 days after treatment. **Method:** We analyzed 124 consecutive ICH patients with 90-day outcome data who were enrolled in a prospective cohort study between 2006 and 2009. Eighty-three patients were included in this study. Among ICH survivors, univariate Cox regression models and Kaplan-Meier plots were used to determine subject characteristics that were associated with an increased risk of recurrence. Statin usage was determined through interviewing the patient at the time of ICH and confirmed by reviewing their medical records. Independent status was defined as Glasgow Outcome Scale grades 4 or 5. **Results:** Were statin users 20/83 (24%) patients before the ICH. There was no effect from pre-ICH statin use on the functional independence rates (32% versus 36%, $P=0.79$) or mortality (41% versus 47%, $P=0.82$). **Conclusion:** Pre-ICH statin use is not associated with changes to ICH functional outcome or mortality. **Key words:** cerebral hemorrhage, hydroxymethylglutaryl-CoA reductase inhibitors.

Prognóstico da hemorragia intracerebral em pacientes previamente tratados com estatinas

RESUMO

Objetivo: Inibidores da 3-hidroxy-3-methylglutaryl coenzima A (HMG-CoA) redutase, ou estatinas, têm sido associados com melhora do prognóstico após eventos encefálicos isquêmicos e hemorragia subaracnóidea, mas com um aumento do risco de evento encefálico hemorrágico (AVEh). Nós investigamos se o uso de estatinas prévio ao sangramento é associado com independência funcional em 90 dias. **Método:** Analisamos 124 pacientes consecutivos com AVEh com 90 dias de seguimento, selecionando 83 para um estudo coorte prospectivo entre 2006 e 2009. O uso de estatinas foi determinado pela entrevista ao paciente no momento da entrada ao hospital e complementado pela revisão do prontuário. Foi definido como independência funcional um GOS (Glasgow Outcome Scale) 4 ou 5. **Resultados:** Estatinas eram usadas por 20/83 (24%) antes do AVEh. Não houve efeito benéfico do uso prévio ao AVEh de estatinas nas taxas de independência funcional (32% versus 36%, $P=0,79$) ou mortalidade (41% versus 47%, $P=0,82$). **Conclusão:** O uso de estatina pré-AVEh não é associado com melhora do prognóstico funcional ou taxa de mortalidade.

Palavras-chave: hemorragia cerebral, inibidores de hidroximetilglutaril-CoA redutases.

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Intracerebral hemorrhage (ICH) causes first-time stroke in 10% to 15% of such patients, with a 30-day mortality rate of 35% to 52%; half of the deaths occur in the first two days¹⁻³. In one population study on 1041 cases of ICH, 50% had a deep location, 35% were lobar, 10% were cerebellar and 6% were in the brain stem⁴. The mortality rate one year after ICH varies according to the location of the ICH: 51% for deep hemorrhage, 57% for lobar, 42% for cerebellar and 65% for brain stem⁵. Out of the estimated 67,000 patients who had an ICH in the United States during 2002, only 20% are expected to be functionally independent six months later³.

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have other effects in addition to decreasing cholesterol synthesis⁶. Statin-treated animals have better outcomes in experimental models for ischemic stroke⁷ and intracerebral hemorrhage (ICH)^{8,9}. Human studies suggest that statins are associated with better outcomes after ischemic stroke¹⁰ and subarachnoid hemorrhage¹¹.

In contrast, it is not known whether pre-ICH statin use confers better outcomes among patients with ICH. Some of the pleiotropic effects of statins, such as decreased platelet aggregation¹² and decreased thrombogenesis¹³, may promote hematoma expansion or increase the risk of recurrent hemorrhage.

Therefore, we investigated whether prior use of statin would improve the outcome among patients with ICH.

METHOD

We retrospectively analyzed data from an ongoing single-center prospective longitudinal cohort study on primary ICH. All patients with a baseline admission CT scan and determination of functional status at 90 days were eligible. Clinical information, including medication use and dosage, was abstracted from the medical records and supplemented by interview. ICH volume and location were determined by means of computer-assisted segmentation. This study was approved by the local ethics committee.

There were 124 consecutive admissions with symptom onset between January 1, 2006 and December 31, 2010. Baseline CT scan was not performed or was missing in 8/124 (0.6%), and other data were missing in 5/124 (0.4%), leaving 111 subjects with complete baseline information. Death within 30 days occurred in 28/111, thus leaving 83/111 30-day survivors. Therefore, 90-day Glasgow outcome scale (GOS) was determined for a total of 83/124 potential subjects (67%).

Independent status was defined as GOS 4 or 5. Logistic regression models were constructed to determine whether pre-ICH statin use was associated with independent status or mortality. Age and Glasgow coma

Table. Some data from the patients according to presence of statin use before ICH.

Characteristic	Statin n=20 (24%)	No statin n=63 (76%)	P
Median age (SD)	68 (8.2)	69 (7.6)	0.73
GCS (variation)	11 (6-15)	12 (6-15)	0.89
GOS 4 or 5 (90-day independence)	32%	36%	0.79
90-day mortality	41%	47%	0.82

GCS: Glasgow coma scale; GOS: Glasgow outcome scale.

score (GCS) score were categorized according to cutoff points that were established in univariate analysis, as follows: [1] age: <69, 70 to 79 and >80, [2] GCS: 3 to 10, 11 to 14 and 15.

Among the ICH survivors, univariate Cox regression models and Kaplan-Meier plots were used to determine subject characteristics that were associated with an increased risk of recurrence. Post-ICH statin use was analyzed as a time-dependent variable because some subjects started or discontinued statins during the follow-up period. Post-ICH statin use and any variables associated with ICH recurrence ($P < 0.20$) were entered into a multivariable Cox regression model, followed by backward elimination of nonsignificant variables ($P > 0.05$). Statistical analyses were performed using SAS version 9.1.3.

RESULTS

Were statin users 20/83 (24%) patients before the ICH. There was no effect from pre-ICH statin use on the functional independence rates (32% versus 36%, $P = 0.79$) or mortality (41% versus 47%, $P = 0.82$). Medical comorbidities and warfarin use were more common in statin users. The multivariable-adjusted odds ratio for independent status in pre-ICH statin users was 1.03 (95% CI: 0.71 to 2.21, $P = 0.71$).

Pre-ICH statin use was not associated with independent status or mortality (Table). We considered whether the effect of statin use might vary according to outcome definition or patient subgroups. There was no difference in 30-day or 90-day survival in pre-ICH statin users (data not shown). Because statin withdrawal may worsen stroke outcome^{14,15}, we performed additional analyses after subtracting subjects among whom statins were discontinued ($n = 12$) or adding subjects among whom statins were started ($n = 15$). However, the sample did not have enough power to allow definitive conclusions.

DISCUSSION

The initial experimental evidence generated from animals appeared in a couple of studies in 2004. In one

of them, atorvastatin was administered orally beginning 24 h after ICH and was continued daily for one week. With a low dose of 2 mg/kg, a significant reduction in neurological deficit two to four weeks after the ICH was observed, while a higher dose of 8 mg/kg did not improve functional outcome or reduce the brain damage¹⁴.

Supported by these studies, initial attempts to evaluate the effect on humans were made. In a retrospective study performed at Johns Hopkins Hospital, the effect of statin administered prior to ICH was assessed among 125 consecutive ICH patients. The authors found that patients with prior statin use had less perifocal edema than did those without prior statin use. The multivariate analysis showed a significant correlation between prior statin use and reduction of early absolute edema volume¹⁵. The same group demonstrated that prior use of statins was associated with lower mortality at 30 days.

We did not detect any difference in outcomes among patients taking statins before ICH, even after adjustment for medical comorbidities. In contrast, treatment with statins improved sensorimotor recovery in two animal models for ICH^{8,9}. However, there may be biological differences between animals and humans regarding the type of injury that occurs after ICH. In contrast to the animal studies, our subjects were taking various types and doses of statins. A recent study suggested that statins are associated with decreased 30-day mortality but not with improved functional outcome^{16,17}. In our study, pre-ICH statin use had no effect on 30-day mortality. It is unclear whether the different results occurred because of the play of chance, or because of differences in the populations studied.

The main limitation of our study is that statin use was not randomly assigned, and therefore associations between statins and either ICH outcomes or recurrent ICH may be confounded with other factors that are associated with statin use, even though we adjusted for recognized confounders using regression models.

Our analysis of the dose-response effect of statins on ICH outcomes uses the simplistic assumption that maximum dose strengths are equipotent across different drugs.

These data come from a not-so-large series of consecutive ICH cases with functional outcome data and prospective follow-up and therefore provide a best estimate of the effect of statins on ICH outcomes in the absence of large trials. FitzMaurice calculated that a trial of statins to improve 90-day outcome should include 1026 subjects (randomized 1:1 to treat with statin or placebo),

for it to get 90% power to detect an OR >1.24, for independent status in the statin arm¹⁸.

It is too early to come to any conclusion. In addition, because of the small sample size of the present study, and because the underlying prospective study does not define the statins that were used, no definitive conclusion can be drawn until a comprehensive, double blind, prospective study is performed.

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Dear Editors,

Ref. Article: Romero FR, Bertolini E, Vellozo VN, Venturini L, Figueiredo EG. Outcomes from intracerebral hemorrhage among patients pre-treated with statins. *Arq Neuropsiquiatr* 2011;69:452-454.

Some similar points have been observed between our paper and other by FitzMaurice et al. Effect of Statins on Intracerebral Hemorrhage Outcome and Recurrence. *Stroke* 2008; 39:2151-2154. These points are not coincidental but resulted from mistakes when the documents were selected and sent to the editor. So, instead of selecting my own results, I sent a file with graphic and words containing the data from the table of the Fitz Maurice's paper from which I intended to compare my data and present my results. Consequently, my data have not been published but just the Fitz Maurice's results have been displayed as they were mine. I take the total responsibility about this oversight. The Department of Neurology, the Division of Neurosurgery and the Post Graduation program of the University of São Paulo and their personnel have no responsibility for this inaccuracy, as this article was designed and developed in other institution.

I would like to convey my regrets and apologies about this inopportune misunderstanding. Should I had been more meticulous in my revision of the documents before sending them and when I received the proofs, it would have not occurred. The *Stroke* paper was the initial inspiration for my work and it was actually used as reference that I now would like to include. I present a new table displaying my actual data and revision of the text to replace that that was portrayed before.

Replace Table 1 for the following:

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In the sentence:

"We calculated that a trial of statins to improve ...

Change to:

FitzMaurice calculated that a trial of statins to improve 90-day outcome should include 1026 subjects (randomized 1:1 to treat with statin or placebo), for it to get 90% power to detect an OR >1.24, for independent status in the statin arm¹⁸.

In the sentence:

"Statins were used ...

Change to:

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Include a new reference:

18. FitzMaurice E, Wendell L, Snider R, et al. Effect of Statins on Intracerebral Hemorrhage Outcome and Recurrence. *Stroke* 2008; 39:2151-2154.

Best regards,

Flávio Ramalho Romero