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SPANNING THE GLOBE

Vasospasm and Statin Therapy: Yet Another Cautionary Tale

Alejandro A. Rabinstein

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Independent of their cholesterol-lowering effects, statins also have pleiotropic effects which include downregulation inflammation and upregulation of endothelial nitric oxide synthase [1, 2]. Based on this premise, they have been studied in experimental models of subarachnoid hemorrhage (SAH), which showed that statins might ameliorate the mechanisms involved in the generation of vasospasm [1, 3–5]. Various retrospective cohort studies reported discrepant results: some suggested that statin use the time of SAH was associated with markedly lower risk of vasospasm [6, 7], others found no significant difference in vasospasm risk between statin users and non-users [8, 9], and one showed greater risk of vasospasm among statin users, although abrupt statin withdrawal was considered a possible explanation for this finding [10].

Prospective clinical studies soon followed (Table 1). A phase II trial evaluated the role of statins in 80 patients with aneurysmal SAH randomized to receive pravastatin (40 mg daily) or placebo for 14 days [11]. Significant reductions in the incidence of vasospasm (52% vs. 62%) and severe vasospasm (23.5% vs. 30%) defined by TCD were noted among patients treated with pravastatin. The duration of impaired autoregulation was also significantly shorter in the pravastatin group. Vasospasm-related delayed ischemic deficits (DID) occurred in 2 patients in treatment group and 12 patients in placebo group; thereby the incidence of vasospasm-related DIDs was significantly reduced in the pravastatin group by 83%. A subsequent analysis of these investigators showed that there was a strong trend toward better functional outcome at 6 months in the pravastatin group [12]. There was also an 88% reduction in all-cause mortality; none of the patients in pravastatin-treated group died of vasospasm-related complications, while 12.5% of deaths in the placebo group were attributed to vasospasm. Physical and psychosocial outcomes at 6 months were better in pravastatin-treated patients on multivariable analysis.

Three other smaller randomized studies have been published with diverse results. Lynch et al. randomized 39 patients to receive simvastatin 80 mg or placebo for 14 days and found a statistically significant reduction of ultrasonographically defined vasospasm in the simvastatin group (26% vs. 60%) [13]. Chou et al. also randomized 39 patients with Fisher grade 3 SAH to simvastatin 80 mg or placebo for up to 21 days, but the results of this study did not show any significant difference between the groups in the rates of vasospasm, vasospasm-related infarcts, or mortality [14]. Although there was a trend toward less vasospasm in the statin group, simvastating-treated patients exhibited a tendency to have worse functional outcomes [14]. Meanwhile, Vergouwen et al. enrolled 32 patients in a randomized study comparing simvastatin 80 mg versus placebo until day 14 after SAH [15]. The main objective of this exploratory study was to investigate the biological effects of statin therapy. Statin-treated patients had reductions in total cholesterol and LDL-cholesterol levels, but were similar to control patients in various parameters of coagulation, fibrinolysis, endothelial function, and inflammation [15]. Statin therapy was safe in all these small trials; specifically, there were no severe cases of myositis or hepatitis reported [11, 13].

The mixed nature of the results of these small prospective randomized, placebo-controlled trials is only one of the arguments for caution. Centers that modified their

A. A. Rabinstein (✉)
Division of Critical Care Neurology, Department of Neurology, W8B, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA
e-mail: rabinstein.alejandro@mayo.edu

Table 1 Prospective clinical studies evaluating statins in the treatment of aneurysmal subarachnoid hemorrhage

Study	Design	Statin type and dose	Population size	Main results
Tseng et al. [11, 12, 21]	Randomized, placebo-controlled	Pravastatin 40 mg/day	80	Reduced vasospasm Reduced severe vasospasm Lower duration of impaired autoregulation Reduced DID related to spasm Improved mortality Improved functional outcome
Lynch et al. [13]	Randomized, placebo-controlled	Simvastatin 80 mg/day	39	Reduced symptomatic vasospasm Attenuated serum markers of brain injury
Chou et al. [14]	Randomized, placebo-controlled	Simvastatin 80 mg	39	No difference in vasospasm, DCI, or functional outcome
Vergouwen et al. [15]	Randomized, placebo-controlled	Simvastatin 80 mg/day	32	No difference in vasospasm, DCI, or functional outcome Better lipid panel, but no difference in other laboratory markers
Kramer et al. [17]	Observational, historical control	Simvastatin 80 mg/day	150	No difference in vasospasm, DCI, or functional outcome
McGirt et al. [18]	Observational, historical control	Simvastatin 80 mg/day	340	No difference in symptomatic spasm, functional outcome, in-hospital mortality, or LOS
Kern et al. [16]	Observational, historical control	Simvastatin 40 mg/day	130	No difference in vasospasm, symptomatic spasm, or functional outcome and mortality at discharge

DCI delayed ischemic deficits, *DCI* delayed cerebral infarctions, *LOS* length of hospital stay

practice and began administering statin therapy to all their patients with SAH after the first reports indicating beneficial effects of statin use on vasospasm have subsequently reported lack of improved outcomes among statin-treated patients compared with historical controls treated at the same institutions before the change in practice [16–18]. Although preliminary data on the use of statins for the prevention of severe vasospasm appear encouraging [19, 20], early promising results must be confirmed on larger, multicenter trials (such as the ongoing STASH trial) before statins can be recommended for this indication.

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