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Clinical Study

Statins may not protect against vasospasm in subarachnoid haemorrhage

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ABSTRACT

Statins have been shown in two recent small phase I/II trials to be associated with a marked reduction in clinical and transcranial Doppler (TCD) evidence of vasospasm after aneurysmal subarachnoid haemorrhage (SAH). The purpose of this study was to assess the clinical impact of this treatment in a larger number of patients. Fifty-eight individuals were treated in the year before, and 72 patients treated in the year after, the introduction of a 2 week course of 40 mg/day pravastatin therapy for SAH. Statins did not result in reduced TCD velocities, clinical or angiographic vasospasm, or improvements in global outcome at the time of hospital discharge. A measurable reduction in the rates of vasospasm was expected, based on the size of the effect of statin therapy in the previous small studies. There remains significant uncertainty as to the role of statins in preventing vasospasm after SAH.

1. Introduction

Nitric oxide depletion and dysfunctional endothelial nitric oxide synthase (eNOS) within cerebral vessels is thought to contribute to symptomatic cerebral vasospasm after aneurysmal subarachnoid haemorrhage (SAH).[1–3] The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, known as statins, may be neuroprotective by up-regulating eNOS mRNA expression.[4] This leads to increased nitric oxide production within endothelial cells, dilating cerebral arteries and thus promoting increased cerebral blood flow. Statins may have additional neuroprotective effects independent of their influence on eNOS.[5,6] Experimental statin therapy in animal models of SAH-induced vasospasm has excited optimism about clinical application to secondary prevention of SAH-induced vasospasm.[7–10] Some studies[11,12] of patients being treated with statins prior to SAH demonstrate protection against symptomatic vasospasm but another[13] found that prior statin use increased the risk of vasospasm. Phase I/II randomized placebo-controlled trials in the UK[14] and the USA,[15] with statin treatment groups of just 40 patients and 19 patients respectively showed at least 30% reduction in the incidence of vasospasm and a 70% to 83% reduction in delayed ischemic neurological deficits and mortality. Because of the long track-record of safety in oral statin intake and a low incidence of side effects with these drugs in the treatment of dyslipidaemia and atherosclerosis,[16] and the size of the effect of vasospasm prevention in the two trials, we introduced statin therapy in our institution. Our protocol reproduced the Tseng et al. regimen,[14] which we felt was supported by the most robust data available in October 2005. The current study assesses the clinical and radiological outcomes achieved with a 2-week course of pravastatin therapy commencing at the time of admission with SAH.

2. Materials and methods

An institutional policy that ensures that patients admitted with aneurysmal SAH receive 40 mg of pravastatin per day by nasogastric or oral route was started on 14 October 2005. The patients included in this study were admitted 12 months before and 12 months after implementation of the statin policy at the West Australian Neurosurgical Service, Royal Perth Hospital. There were no other significant changes to the management of these patients during this time.

We studied 135 consecutive patients with ruptured cerebral aneurysms who survived long enough to undergo invasive (catheter) or non-invasive studies (CT scan, magnetic resonance angiography [MRA]) and who were not already on statin therapy. Fifty-eight patients were managed in the pre-statin era and 72 patients in the statin era. We excluded an additional 5 patients who presented during the study but were already taking statins for other conditions. However, we included, as part of an intention-to-treat philosophy, three patients managed in the statin era but who failed to receive statins.

Univariate analysis showed no significant differences between the pre-statin and statin era patients with regard to demographic

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Table 1
Demographic, subarachnoid haemorrhage and treatment details in patients in the pre-statin and statin eras

		Pre-statin era (mean ± SE; $n = 58$)	Statin era (mean ± SE; $n = 72$)	p value (statistical test)
Mean age (y)		51 ± 1.70	54 ± 1.56	0.27 (t-test)
Sex ratio (M:F)		0.66	0.39	0.15 (χ^2)
World Federation of Neurosurgical Societies Grade (no. of patients)	G1	28	35	0.45 (χ^2)
	G2	8	17	
	G3	6	3	
	G4	3	4	
	G5	13	13	
Fisher Grade (no. of patients for each grade)	G1	1	1	0.57 (χ^2)
	G2	17	15	
	G3	24	26	
	G4	16	30	
Proportion with hydrocephalus		0.50	0.53	0.75 (χ^2)
Proportion with intraventricular haemorrhage		0.28	0.38	0.23 (χ^2)
Proportion with intracerebral haemorrhage		0.17	0.17	0.93 (χ^2)
Aneurysm location (fraction of total)	ACom	0.36	0.33	0.89 (χ^2)
	PCom	0.17	0.19	
	MCA	0.19	0.22	
	ICA	0.16	0.11	
	VB	0.052	0.097	
	Other	0.035	0.042	
Surgical treatment modality (fraction of total)	Clip	0.35	0.42	0.55 (χ^2)
	Coils	0.57	0.47	
	None	0.035	0.042	
Proportion treated with ventricular drainage		0.55	0.44	0.22 (χ^2)
Days since SAH onset at admission		1.3 ± 0.4	1.0 ± 0.3	0.63 (t-test)
Mean number of days since SAH onset at time of aneurysm clipping or coiling		2.9 ± 0.5	2.6 ± 0.4	0.64 (t-test)

Standard errors (SE) are included for continuous data. χ^2 = Chi-squared test.
ACom = anterior communicating artery, ICA = internal carotid artery, MCA = middle cerebral artery, PCom = posterior communicating artery, SAH = subarachnoid haemorrhage, VB = vertebrobasilar.

features, severity or nature of SAH, risk factors for vasospasm, location of aneurysm, or surgical/endovascular treatment modalities (Table 1). The biggest difference between groups was the male to female ratio, 0.66 in the pre-statin era and 0.39 in the statin era, but this was not statistically significant ($p = 0.15$).

At the time of discharge we performed a retrospective review of patient notes, transcranial Doppler (TCD) recording sheets, CT scan and digital subtraction angiogram images and reports, and reviewed prospectively obtained modified Rankin Scores (mRS).[17]

2.1. Statistical methods

We performed parametric and, where appropriate, non-parametric univariate analysis. The two-tailed paired and unpaired Student's t-test (with Welch's correction and satisfaction of F tests) was used to compare continuous data between the pre-statin and statin eras. When the F tests were not satisfied, the Mann-Whitney non-parametric test for significance was used. One-way ANOVA with satisfaction of Bartlett's test for equal variances and the Newman-Keuls multiple comparison post-test was used to compare utilization of left versus right MCA TCDs in both the pre-statin and statin eras. The sample size and event rates in this study were sufficient to use a two-sided Chi squared (χ^2) contingency analysis to compare categorical data between the pre-statin and statin eras. Standard errors are used to indicate variance. GraphPad Prism 4.00 for Windows (GraphPad Software, San Diego, CA, USA) was used for statistical analysis. Alpha was taken as 0.05.

3. Results

Pre-statin era and statin era patients showed no significant differences in rates of clinical or angiographic vasospasm. Clinical vasospasm was defined as focal neurological deficits not explained by hydrocephalus, surgical trauma, or new haemorrhage by the treating neurosurgeon or resident. Angiographic spasm was defined as evidence of more than 50% narrowing of the internal carotid, basilar, anterior cerebral, middle cerebral or posterior cerebral arteries on catheter angiography. These angiograms were from either the admitting or treatment study or subsequent studies performed when clinical vasospasm occurred that was unresponsive to hypervolemic, hypertensive and hemodilutional therapy. In the pre-statin era, 25 of 58 patients had clinical and/or catheter-angiographic vasospasm, whereas in the statin era, 29 of the 72 patients had clinical and/or angiographic vasospasm, which is not significantly different to the rate in the pre-statin era ($p = 0.75$, Table 2).

TCDs were obtained in 48 of 58 pre-statin era patients and 57 of 72 statin era patients ($p = 0.61$) by the same specialized neuro-ultrasonographers over both periods. A mean (± SE) of 8.4 ± 0.8 separate unilateral MCA recordings were made in each pre-statin patient compared with 10.4 ± 0.9 recordings per patient in the statin era ($p = 0.10$). Paired right and left recordings were made in all but 4 of the patients undergoing TCD studies. TCD measurements were made either routinely or if there was particular concern about the patient's vasospasm risk depending on the opinion of the treating clinicians and included both raw MCA velocities and extracranial internal carotid artery (ICA) velocities for calculation of Lindegaard ratios.[18] The left MCA TCDs were obtained an average (± SE) of 4.1 ± 0.4 times during the 21 days following SAH in the pre-statin era. This did not differ significantly from utilization of right MCA TCD recordings in the same period (4.3 ± 0.4) or the left (5.2 ± 0.4) or right (5.2 ± 0.4) MCA TCDs in the statin era ($p = 0.15$, multiple comparisons all $p > 0.05$). Thus there appears to have been a consistent utilization of left and right MCA TCDs over both treatment eras.