

Initiation Of Statin Therapy - Lack Of Effect On MR Spectroscopy And Cerebral Perfusion

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Citation

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Abstract

Statin has been indicated to have a positive side effect of improving memory and helping the Alzheimer patients. Here we studied the brain perfusion and spectroscopy of volunteers who took Lipitor and compared them to the ones who did not have the pile. The result did not show any significant difference in between the two groups.

INTRODUCTION

Statin drugs are used clinically to lower serum cholesterol levels and appear to have interesting side effects [1-4], including changes in vasoreactivity and increases in cerebral blood flow in animal models [2, 5] and in humans [6-7]. However, some studies have shown no measurable effect on blood flow in post-stroke patients [8-11].

It has been postulated that Statins slow the development of dementia [7, 12], although the effect has been difficult to document. If statins do effect the progression of dementia, the effect could be caused by increasing cerebral blood flow (CBF), or increasing neurotransmitter activity. Statins have been associated with increases in blood flow in the heart and a few other parts of the body [15-17], but not in the brain. Although statins have been found to reduce the long-term risk of stroke [18], studies of statins in stroke patients did not show any significant change in CBF [19-20].

We evaluated the secondary effects of statins on the brains of asymptomatic individuals at the initiation of statin therapy and of a change in diet by using regional vertebral blood-flow analysis and MRI spectroscopy.

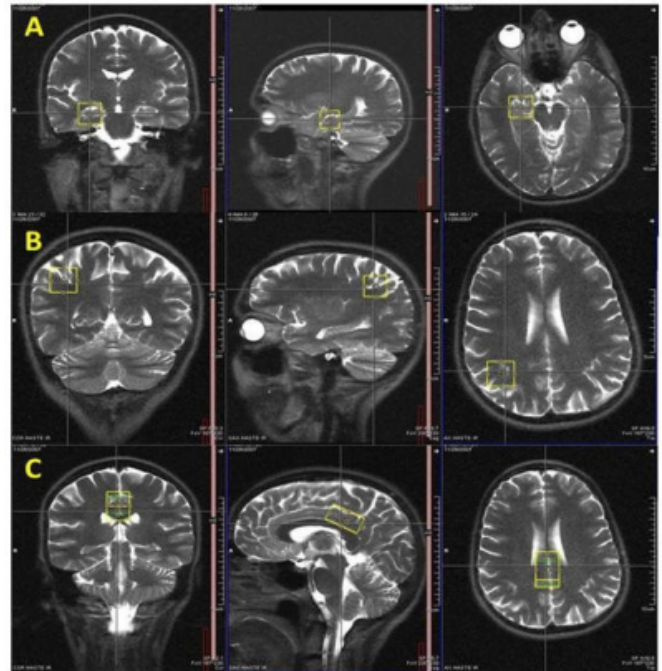
MATERIALS AND METHODS

Eighteen volunteers with high blood cholesterol (otherwise healthy) were recruited and were given a choice to lower their blood cholesterol by diet or pills. The first group opted to use a statins (Lipitor® 20mg) to lower their cholesterol levels, while the second group preferred to try to reduce their cholesterol levels with diet alone. All volunteers went through a screening test and a baseline MRI-MRS. After three months of taking Lipitor or of being on the cholesterol-lowering diet, a follow-up MRI was performed. The MRI

consisted of fast T2 images used as localizers for spectroscopy followed by an EPI-based brain perfusion (T2*) sequence.

Figure 1

Locations of the three voxels used in the study. A: hippocampus, B: parietal cortex and C: posterior cingulated gyrus.

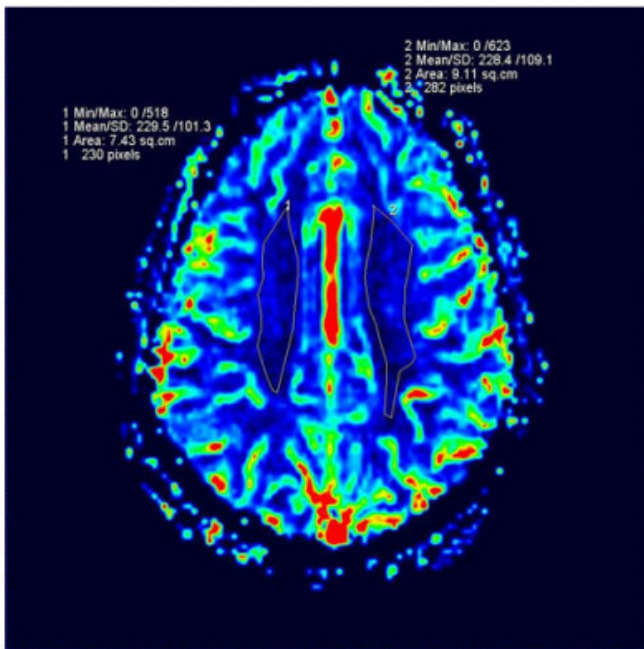


A single-dose contrast agent was administered during the perfusion sequence. The injection rate was 5cc/sec and was injected at the 8th measurement. The total number of measurements for the perfusion series was 50. After perfusion, Single Voxel Spectroscopy was performed at

three different locations in brain: the hippocampus, parietal cortex and posterior cingulated gyrus as shown. The voxels dimensions were 20×20×20 mm³ for the first two locations and 15×20×30 mm³ for the posterior cingulated gyrus (to better fit the anatomy). All the spectra were obtained with TR=3 sec and TE=30 msec. Each spectroscopy sequence was followed by an unsuppressed water series (for quantification purposes).

Figure 2

Slice from a subject’s rCBV series. The ROI drawn is healthy white matter to obtain “avgWM” for normalization.



The spectra were post-processed on the scanner console and off line with LC-Model [21]. The perfusion data was transferred to an off-line Siemens workstation and post processed with Siemens perfusion software to obtain relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF). The rCBV was then normalized with respect to healthy appearing cortical white matter for more accurate comparison among subjects [22]. The normalization was done as follows: the average healthy appearing cortical white matter (avgWM) was measured by drawing ROIs on rCBV (Fig. 2). The rCBV series was divided by this number (avgWM) resulting in a normalized CBV series. The pixel value of this series (normalized CBV) is the ratio of the rCBV pixel divided by cortical white matter rCBV. Any ROI drawn on the normalized CBV shows the ratio of the CBV of that tissue to that of healthy appearing cortical white matter. This eliminates the changes from one time point to the next and makes the comparison of perfusion among

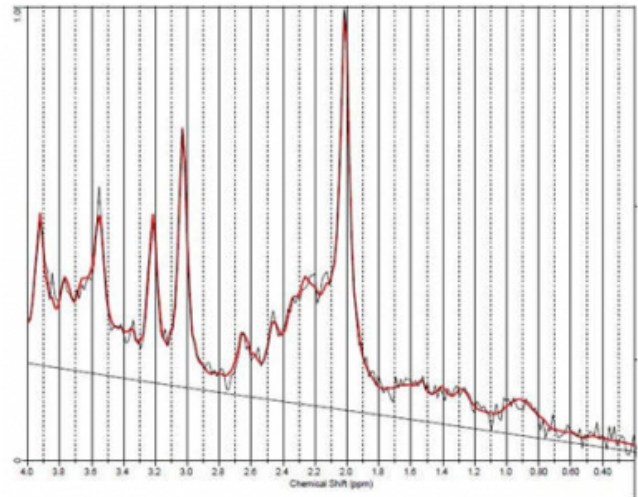
subjects easier and more meaningful.

RESULTS:

MRS: The spectra from all three locations were analyzed. A typical spectrum with the LC Model fit (red line) is shown in figure 3.

Figure 3

The Spectra of a subject’s posterior cingulated gyrus. The red line is the LC Model fit to the actual spectra (black).



We measured the concentrations of N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), inositol (mI) and combined glutamine + glutamate (Glx) for all voxels. The results are presented in Table 1 and also in Fig.4. Comparing all the metabolite concentrations for both time points, we found no significant change between the initial scan and the three-month follow-up in either group.

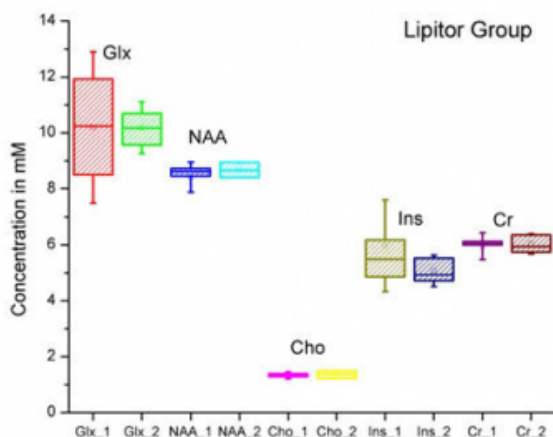
Table 1

The mean and standard deviation of hippocampus metabolites concentrations (in mmol) for both the groups at baseline and the 3 month follow-up scan.

| Spectroscopy | Diet Group | | Lipitor Group | |
|--------------|--------------|-------------|---------------|--------------|
| | Base-line | Follow-up | Base-line | Follow-up |
| NAA | 8.76 ± 0.68 | 7.95 ± 0.46 | 8.42 ± 0.54 | 8.67 ± 0.26 |
| Cr | 5.69 ± 0.79 | 5.61 ± 0.53 | 5.96 ± 0.48 | 6.04 ± 0.36 |
| Cho | 1.29 ± .020 | 1.28 ± 0.11 | 1.15 ± 0.13 | 1.36 ± 0.14 |
| Glx | 10.78 ± 0.53 | 9.49 ± 1.85 | 10.19 ± 2.70 | 10.18 ± 0.93 |
| Ins | 5.03 ± 0.62 | 4.74 ± 0.64 | 5.97 ± 1.64 | 5.07 ± 0.56 |

Figure 4

Statistical Box graph of the concentration of metabolites for the Lipitor group subjects for both time points: 1 is baseline and 2 is three-month follow-up.



Perfusion: The normalized CBVs were measured at 8 locations (ROIs): two were in the hippocampus and six were in cortical gray matter (Fig. 5) in the cerebral hemispheres. The values were tabulated and analyzed. Table 2 showed the mean and standard deviation of these normalized CBV for all the ROIs. Statistical analysis (t-test) confirmed that there was no significant change at any measured location, between the two time points in either group.

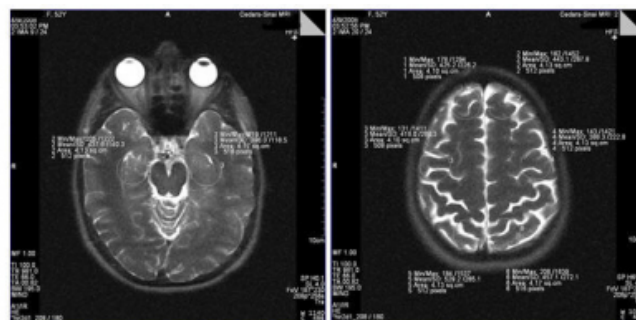
Table 2

Normalized CBV mean & standard deviation in the areas shown in figures 5 & 6, for both groups, at the baseline and 3 months follow-up.

| perfusion | Diet Group | | Lipitor Group | |
|--------------|-------------|-------------|---------------|-------------|
| | Base-line | Follow-up | Base-line | Follow-up |
| Rt_hippo | 4.88 ± 0.95 | 4.67 ± 0.71 | 5.98 ± 1.41 | 6.21 ± 1.33 |
| Lt_hippo | 4.71 ± 1.31 | 4.77 ± 1.05 | 6.40 ± 2.14 | 5.72 ± 0.86 |
| Rt_frontal | 5.23 ± 3.32 | 4.77 ± 1.89 | 3.85 ± 1.49 | 4.00 ± 1.71 |
| Lt_frontal | 4.50 ± 1.86 | 4.45 ± 1.71 | 4.12 ± 1.36 | 4.40 ± 1.92 |
| Rt_parietal | 5.46 ± 2.33 | 6.08 ± 2.13 | 6.20 ± 2.54 | 4.85 ± 2.16 |
| Lt_parietal | 5.55 ± 3.84 | 5.02 ± 2.66 | 6.13 ± 1.72 | 5.55 ± 2.42 |
| Rt_occipital | 5.04 ± 2.01 | 5.35 ± 1.72 | 5.65 ± 2.41 | 5.50 ± 1.87 |
| Lt_occipital | 5.21 ± 1.71 | 4.55 ± 2.12 | 5.52 ± 2.47 | 4.92 ± 2.14 |

Figure 5

Circular ROIs to measure perfusion in the hippocampus (left) & in cortical gray matter (right).



CONCLUSION

The study showed no significant changes in the levels of brain metabolites or cerebral blood volume between the baseline and the three-month follow-up for the Lipitor group and for the diet group. The negative results could be due to: 1) small sample size, 2) time between the baseline and follow-up scan is not enough to detect changes, 3) change (if any) in CBV or metabolites concentrations is extremely small compared with normal fluctuations (noise) as can be seen from large values of standard deviations, or 4) statins have no effect on the cerebral metabolites concentrations and perfusion.

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