Optimization of USPIO enhanced in vivo MRI of human carotid atherosclerosis

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Synopsis

We have optimized the timing and sequences of Ultrasmall Superparamagnetic Particles of Iron Oxide (USPIO) enhanced magnetic resonance (MR) imaging of the carotid arteries in 8 patients scheduled for carotid endarterectomy. Patients underwent MR imaging before, 24, 36, 48, 72 and 96 hours after infusion of the USPIO agent, Sinerem®. USPIO induced a signal decrease within the atheromatous plaque on 2D spiral T_2*W images of the carotid artery. The decrease in signal intensity was seen as early as 24 hours but was maximal at 48 hours post infusion. Immunohistochemical analysis of excised plaques revealed co-localisation of iron and activated/immature macrophages.

Background

Distinguishing between those atheromatous plaques that are likely to rupture and thought unstable from those thought to be stable and less likely to rupture remains a challenge in more accurately selecting patients suitable for carotid endarterectomy or alternative therapeutic interventions. Histological data has revealed a preponderance of inflammatory cells, mainly macrophages, within plaques determined to be unstable by gross macroscopic features. It has only recently been possible to use imaging modalities to accurately define areas of macrophage content in humans in vivo (Rudd et al, 2002). Animal studies have revealed that USPIO can induce focal signal intensity decreases on T_2W MR images in the walls of atherosclerotic plaques (Schmitz et al. 2001). Furthermore, small pilot data have revealed similar findings in the human carotid artery (Kooi et al, 2002). What has yet to be fully established is the precise timing of MR imaging following the infusion of USPIO and the optimal sequences for detecting the decrease in signal intensity. In the present study we undertook to optimize the sequence protocol and timing of USPIO MR imaging using the USPIO agent, Sinerem ®.

Methods

In vivo MR imaging of 8 patients scheduled for carotid endarterectomy was performed on a 1.5T whole body system (GE Medical Systems, Milwaukee, WI) using a dedicated 4 channel phased array carotid coil. The following pulse sequences were used; 3D T_2*W gradient echo (TR/TE:35/15, pixel size: 0.4x0.8x1mm, matrix = 256x128), 2D T_1W ECG-gated, blood suppressed, fast spin-echo (TR/TE: 1 R-R/ 7.8, pixel size: 0.4x0.4x3mm, ETL=12 matrix: 256x256), 2D T_2*W ECG-gated, blood suppressed spiral (TR/TE:1 R-R/5.6 & 15, effective pixel size: 0.42x0.42x3mm, matrix: 4096x22 interleaves).The USPIO contrast agent (Sinerem ®, Guerbet, Roissy, France) was then given by intravenous infusion and the carotid arteries imaged at 24, 36 48, 72 and 96 hours post infusion using the same MR sequences. Following plaque retrieval at surgery, specimens were fixed in buffered formalin before being embedded in paraffin. Subsequently, 4µm sections were subjected to immunohistochemical analysis, for plaque morphology (Elastic van Gieson (EVG) stain), activated macrophage content (MAC 387immunostain) and iron (PERLs reagent). Electron microscopy was performed in areas of PERLs positive staining. In addition the plaques of 10 patients undergoing endarterectomy without USPIO MR imaging were also obtained to serve as negative controls for the presence of iron in the plaque.

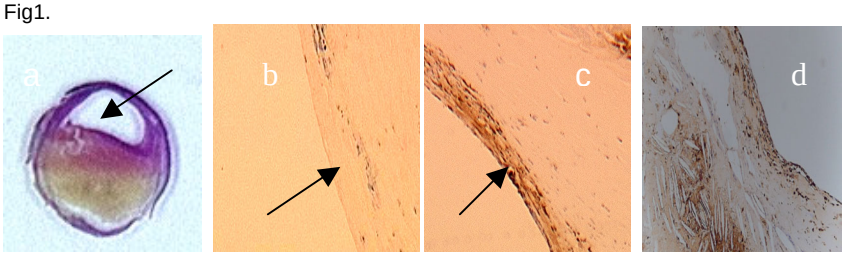
Results

Immunohistochemical analysis confirmed the uptake of USPIO (PERLs stain) into areas of atheromatous plaque where activated macrophages were seen (MAC387 positive staining). No PERLs positive staining was seen in the plaques from patients not given the USPIO agent (Fig 1). In vivo MR imaging following the infusion of USPIO demonstrated focal drop in signal intensity compared with pre-infusion MR imaging (Fig 2), as early as 24 hours. This drop in signal intensity was maximal at 48 hours post infusion though was evident up to 72 hours post infusion. Comparison with histology revealed that the drop in signal intensity was in areas of PERLs positive staining. The changes were maximal on the spiral T_2*W pulse sequence images.

Conclusion

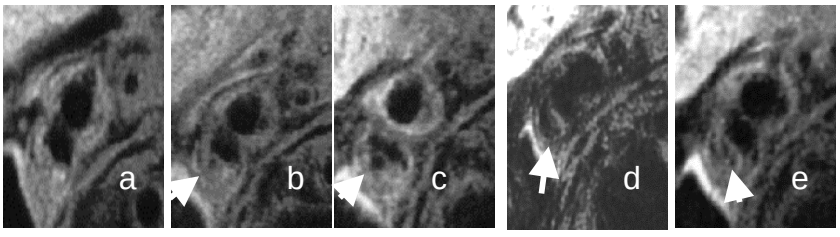
Immunohistochemical analysis revealed that USPIO are taken up by activated macrophages in carotid atheroma. The resulting drop in signal intensity that these particles cause are best seen on the spiral T_2*W gradient echo sequence at 48 hours after infusion of the USPIO agent. The ability to visualise macrophages in atheromatous plaques of patients with carotid artery stenosis may aid better patient selection for carotid endarterectomy or novel alternative therapies.

Fig1.



Corresponding histological sections of internal carotid artery stained with a) EVG, b) PERLs reagent, c) MAC 387 immunostain for activated macrophages from a patient infused with USPIO pre-operatively; d) PERLs reagent and MAC 387 immunostain in a patient without USPIO infusion. PERLs positive staining co localises with areas of activated macrophages in the fibrous cap (arrow) region, following USPIO infusion only.

Fig 2.
Corresponding in vivo T2*W serial MR imaging of the internal carotid artery a) before and following USPIO infusion at b) 24 hours, c) 36 hours, d) 48 hours, e) 96 hours. Focal drop in signal intensity can be visualised at 24 hours (arrow) in the area of the atheroma seen in Fig 1 above(black arrow) and becomes maximal at 48hours (arrow), fading by 96 hours.



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