MRI of the Liver: a Comparison of High-dose and Low-dose Ferumoxide Infusion in Patients with Liver Cirrhosis

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Introduction
In a previous study (1) we compared lesion-to-liver contrast-to-noise ratios (CNR’s) following ferumoxides administration at doses of 15µmol/kg (high-dose) and 7.5µmol/kg (low-dose) in patients with colorectal liver metastases. Although the percentage signal intensity loss (PSIL) of the liver was significantly greater in the high dose compared with the low-dose group, the change in CNR was not significantly different between the two groups because the PSIL of the lesions was also greater in the high-dose group. In patients with liver cirrhosis the uptake of ferumoxides is reduced due to diminished phagocytic activity so our earlier results cannot be extrapolated to this patient population (2,3). The purpose of this study was to compare low-dose and high-dose infusion of ferumoxides using gradient echo imaging at 1.5T in patients presenting with end stage liver cirrhosis.

Methods
The study population comprised 30 liver transplant candidates with end stage liver cirrhosis who underwent ferumoxide enhanced MR imaging. Ferumoxides were administered at a dose of 7.5µmol/kg in 17 patients, 14 men, 3 women (age range 41-72) and at a dose of 15µmol/kg in 13 patients, 8 men, 5 women (age range 35-74). A cohort of 13 patients, 8 male, 5 female (age range 49-73) with colorectal carcinoma liver metastases and normal background liver were also included in the study as a low-dose ferumoxide control group. In all patients the dose of ferumoxides was diluted in 100ml of 5% glucose solution and infused over 30 minutes. Imaging commenced 1-2 hours from the end of the injection. All imaging was performed on a Siemens Symphony MR system at 1.5T (Siemens, Erlangen). In all patients before and after ferumoxides, T2W spoiled gradient echo images (GRE), (TR 159, TE 15.1, FA 30) were acquired using a low bandwidth of 65Hz/pixel to maximise signal-to-noise and flow compensation to minimise motion induced artefact from the aorta and IVC. Quantitative measurements were performed in all cases by a single observer using multiple ROI >2cm in the same position pre and post ferumoxides. A single ROI was placed outside the patient within the line of the phase encoding gradient to measure the system noise on each sequence. If a liver lesion was present then a further ROI was placed over the lesion, taking care not to include the surrounding liver. The PSIL of the liver post ferumoxides based on the mean of the three parenchymal ROI was calculated for each patient using the following formula: PSIL = [(SI post SPIO - SI pre SPIO) / SI pre SPIO] X 100. For those patients in the low-dose cirrhotic group with lesions, lesion-to-liver contrast-to-noise ratio (CNR) was also calculated: lesion-to-liver CNR = [(SI lesion - SI liver) / SI background noise]. Statistical Analysis: data was expressed as the mean PSIL with 95% confidence intervals (CI) pre and post ferumoxides. The Mann-Whitney U test was used to establish any statistically significant difference between the high-dose and the low-dose cirrhotic and low-dose non-cirrhotic groups.

Results
There were no side effects following low-dose or high-dose infusions in any of the cirrhotic patients. In the non-cirrhotic control group 2 patients experienced lower back pain which subsided when the infusion was stopped and did not reoccur when infusion recommenced after approximately 5 minutes. The PSIL for the high-dose cirrhotic and the low-dose non-cirrhotic groups were significantly greater than the low-dose cirrhotic group. The mean PSIL for each group is shown in table 1 and the data for each group depicted in figure 1. Six of the patients in the low-dose cirrhotic group had tumours. The post-ferumoxides lesion-to-liver CNR values in these cases are shown in table 2, along with CNR values from the control (non-cirrhotic) group.

Discussion
In the normal liver about 80% of the injected dose of ferumoxides is extracted by the Kupffer cells. T2 shortening induced by the iron oxide particles leads to a marked loss of signal from liver tissue and an increase in liver/lesion CNR because the signal from malignant lesions (which lack functioning Kupffer cells) is unchanged. In the cirrhotic patient reduced parenchymal perfusion and possibly also decreased Kupffer cell function results in decreased liver uptake of ferumoxides usually associated with increased uptake in the spleen and bone marrow. Furthermore, liver uptake is often heterogeneous due to fibrosis, inflammation and regeneration of liver tissue. The optimum sequence for use with ferumoxides is subject to debate. Although Tanimoto et al (4) recommended T2W FSE images after ferumoxides in patients with cirrhosis we used a T2W GRE sequence in this study. Along with other authors (5) we have found it to be more sensitive than T2 FSE to the effects of ferumoxides. The GRE sequence is also less prone to motion artefacts which maybe severe in patients with end stage cirrhosis due to ascitic fluid and an inability to sustain arrested respiration. In a previous study we showed that a 50% reduction in the dose of ferumoxides caused only a 10% fall in PSIL of normal liver and no significant difference in metastasis-to-liver CNR’s (1). Yamamoto et al (6) found a significant increase in the number of small HCC’s detected after ferumoxides enhancement in patients with cirrhosis. They used three different doses of SPIO (5, 10 & 15 µmol/kg) and found no substantial difference in lesion-to-liver CNR at the different doses. In the current study PSIL was significantly less in our low-dose cirrhotic patients than in our high-dose cirrhotic and low-dose non-cirrhotic groups. Even so, in all 6 cirrhotic patients with tumours, lesion-to-liver CNR’s after low-dose infusions were fairly high, approaching those achieved in our low-dose non-cirrhotic group. Two patients showed little change in CNR after ferumoxides, but in both cases the CNR was high on pre-contrast images.

Conclusion:
Whilst we found a substantial PSIL after low-dose ferumoxides in the majority of our cirrhotic patients (median PSIL, 58.5%) the range of PSIL values was considerably greater than in the other groups and we feel that further studies are needed before a reduced dose can be recommended in this patient population.

References

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<tr>
<th>Table 1</th>
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<tr>
<td>High-dose cirrhotic</td>
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<td>Low-dose cirrhotic</td>
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Table 2
Post-ferumoxides lesion-to-liver CNR in patients with tumours

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Median</th>
<th>Range</th>
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<tr>
<td>Low-dose cirrhotic</td>
<td>11.42</td>
<td>11.2</td>
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Figure 1

[Figure 1: Image of a graph showing lesion-to-liver CNR values for different groups.]