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Detection Sensitivity of MRI Using Ultra-Small Super Paramagnetic Iron Oxide Nano-Particles (USPIO) in Biological Tissues

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***Abstract*— Today, by injecting Iron Oxide based nanoparticles (USPIO) as MRI contrast agents, it is possible to study lymphatic system and some specific tumors and their metastasis. The type of surface coating, and coating characteristics of the nanoparticles are important factors for the biological properties of nanoparticles and their destination target. On the other hand, these properties contribute to different signal intensities. This may confine application of all types of USPIO based contrast agents in routine daily experiments. In this study, the ability of detecting these Particles having various sizes and coating properties was evaluated for MRI applications.**

Signal intensity changes after administration of these particles into tissues have been studied and their detection sensitivity was evaluated using a liver phantom and animal model (rat). IO based nanoparticles of various sizes (8-30 nm) functionalized and coated with various surface polymers such as Dextran and Starch, amine and hydroxide groups, and bear IO particles were used to investigate the signal changes. The optimized pulse sequences for proper demonstration of lymph nodes using these contrast agents were found (T2* FSPGR protocol with fat suppressions). A detection sensitivity of %98 was achieved in most experiments during applying a proper MR protocol. However, the type of surface coating, and coating characteristics such as thickness were shown to be essential factors for MRI signal intensity in both T1 and T2 protocols.

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I. Introduction

Prognosis of malignant disease can be determined by metastasis of initial tumor which may involve lymph nodes in some stages. Imaging methods have important roles in determination of cancer staging, progress of diseases, and accurate diagnosis of lymph nodes and their involvements. MRI and PET are currently used to study lymph nodes. However, each has its own limitation and insensitivity.

Today, by injecting a nano-size contrast agent known as USPIO, and application of MRI, it is possible to study lymphatic system and its nodes more accurately. Although, both the mechanism of uptake of these particles into lymphatic system, and its image formation in MRI are known for sometimes, but the exclusive signal intensity due to this approach is not clear yet. This is partly due to the lack of information about various possible pathways of the particles into the physiological system of the human body, and mostly due to complex response of MRI protocols specially GRE/ T2* based protocols to various types of nanoparticles. The former can be due to some contradicting effects such as high vascular permeability of tumoral tissues and their USPIO based infiltration in time.

Dextran coated Iron Oxides are being used for a long time. As one of initial studies [1], injection of these particles in rat showed a decreased signal intensity in brain tomural regions on MR T2 weighted images. Comparative evaluation of IO particles coated with Starch and Dextran [2] was carried out with some results in favor of a better deposition of Starch based particles in lymph nodes and rather a better signal intensity. In an alternative comparative study [3], effect of different amine and hydroxyl groups on the surface was evaluated in rat liver. The result of this investigation was reported as a prolong life of biophosphonate hydroxide group but with its lower uptake into the liver. Surface modification of superparamagnetic nanoparticles using different coating materials was also investigated by other workers [4-5] for invivo bio-medical applications and MR imaging. Uptake of anionic IO particles (AMNP) was also shown [6] to be more effective than dextran-coated particles, whose property is a function of its surface coating. In an alternative comparative study [7], the Dextran-coated IO (ferrofluid) and metal nanoparticles were used as MR contrast agents. In this

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study, the advantage of using metallic Iron without Dextran coating was revealed due to its better MR relaxation property. The effect of particle size on magnetic properties was also mentioned in this research. Using Fe-based metallic alloys with and without Dextarn coating was also reported [8] for suitable evaluation of liver and spleen in rat. In an alternative study [9], the researchers modified the surface of nanoparticles with small organic acid with the amino group outward. They studied magnetization property and proton relaxation time (T1 and T2) of both amine ($NH3^{+}$) surface modified IO, and hydroxide (-OH) group functionalized nanoparticles [10], for possible application of these particles in MR imaging.

In the current research reported here, the ability of detecting nano size Iron Oxide Particles having various sizes and coating properties was evaluated by routine MRI protocols. Also, signal intensity changes after administration of these particles into tissues have been studied.

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I. Materials and Methods

Detection and sensitivity evaluation of USPIO deposit was first studied using a liver phantom. The optimum protocol to perform this task was found on a 1.5T MRI (GE Signa) system. In vivo studies have been started on Rat. The animal was entirely fixed after anesthesia in MR system, and a high sensitive protocol was designed for small animal studies. In the next step, signal intensity was studied after direct injection of USPIO into Rat tissues. Lymphatic system of Rat was also assessed after systematic injection of these agents.

Iron Oxide Nanoparticles of various sizes 8-30 nm functionalized and coated with various surface polymers such as Dextran and Starch, amine and hydroxide groups' surface modified, and bear IO particles were used to investigate the signal changes from administration of these Nano particles.

The optimized pulse sequence for proper demonstration of lymph nodes using USPIO contrast agent was found to be a T2* FSPGR protocol with fat suppressions using a small surface coil. Other 2D and 3D Gradient Echo protocols; T1 weighted (GRE), and T2 weighted (GRE) was also performed to show a better morphology and characteristic of the node composition.

II. RESULTS and Discussion

Our study showed that FSPGR technique provides enough sensitivity, and gives a proper signal for determination of Rat lymph nodes. 24 hours after USPIO injection, lymph nodes were shown to reveal a marked signal intensity change. Furthermore, T1 weighted (GRE) and T2 weighted (GRE) pulse sequences were shown to be required for determination of anatomic regions of lymph nodes, discrimination of fats in abnormal nodes, and differentiation of abnormal cells from a normal tissue.

After deposition of contrast agents into the tissues of interest (in both phantom and animal studies), a definite signal intensity change was obtained for all types of particles. Even a detection sensitivity (for known phantom data and direct injection in rat) of nearly %98 was achieved in most experiments when we apply a proper protocol set up. However, in some protocols, even a small drift from the optimum imaging parameters led to an unexpected signal change. In this situation, diagnosis might be confused between the tissues with normal USPIO uptake and free USPIO uptake.

However, the type of surface coating, and coating characteristics such as thickness were shown to be important factors for MRI signal intensity in both T1 and T2 protocols. Since the type of coating delineates the type of target tissues where most of IO particles are deposited, it is recommended that a special MR protocol and optimized post processing scheme to be found for each application of Nano particles in MRI studies. In the following studies we are going to look into the effect of Monoclonal Antibody conjugated IO particles on signal intensity changes, as this is our aim in a new research project, and moreover, this is going to be the future application of new contrast agent based MR studies for tumor specific Imaging.

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