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REVIEW ARTICLE

Systematic review: Superparamagnetic Iron Oxide nanoparticles as contrast agents in diagnosis of multiple sclerosis

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Abstract

Several MRI contrast agents (CAs) are used in medical diagnosis that gadolinium (Gd^{3+}) is the most widely used as contrast agents. Unfortunately, its toxicity is due to its inefficiency. In this review, we discuss about the ability of SPIONs in MRI and application in Multiple Sclerosis diagnosis. Superparamagnetic iron oxide nanoparticles (SPIONs) such as magnetite nanoparticles are used as good CAs in recent years because of biocompatibility, low level of toxicity, magnetic properties, simple synthesis and coating to use in medical diagnosis. Uncoated magnetite nanonoparticles are insoluble in water. Hydrophilic coatings result water solubility of nanoparticles and prolonged circulation half-lives of SPION and reduce recognition by RES. SPIONs have an important role in diagnosis of multiple sclerosis (MS) by MRI. SPIONs are MRI contrast agents better than gadolinium because, SPIONs taken up by macrophages but not Gd-nanoparticles

Keywords: *Contrast agent; Diagnosis; MRI; Multiple sclerosis; Superparamagnetic iron oxide nanoparticles*

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INTRODUCTION

Nowadays, MRI is a useful clinical diagnosis tool. In this method, water protons of target tissues were excited by a strong magnetic field and relaxation of proton spins can produce image known MR imaging. These relaxations occur via two processes, longitudinal relaxation (T1) and transverse relaxation (T2) [1].

Values of T1 and T2 relaxation times depend on the type of tissue and the magnetic field strength. Thus, the contrast between healthy and diseased tissues can be achieved by varying number of protons and T1 and T2 relaxation times, similar to NMR [2]. While the T1 and T2 are reduced, the MR images are clearer. Increasing proton density is reduced T1 relaxation time, so we will have hypointense MR images. In the other words, reducing proton density is leading to reduced T2, so gives us MRI with higher intensity [3].

The contrast agent is a substance that used for contrasting tissues by shortening of T1 and T2 relaxation times of protons nearby. Contrast agents should be have long blood circulation time and can be evade the RES system. All of contrast agents have unpaired electrons to show magnetic behavior and relax protons around them [4]. There are two classes of contrast agents, Positive contrast agents and negative contrast agents. Positive contrast agents are paramagnetic substances such as chelates of Gd that by shortening of T1 relaxation time become more clear contrast and Negative contrast agents are superparamagnetic contrast agents that leading to a darker contrast by shortening T2 relaxation time. Iron oxide nanoparticles are negative contrast agents that short the T2 relaxation time and appear hypo intense and black areas in MR images [5-7]. They behave as magnetic substance in presence of external magnetic field and loss magnetic properties outside external

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magnetic field [8, 9]. Compared to Gd^{3+}, iron oxide nanoparticles are more sensitive contrast agent in MR images[10-14]. Of course, free iron is toxic and SPIONs are biocompatible due to surface coatings. This means the administered doses of SPIONs must be low for maintain homeostasis level of iron [15, 16]. Ferumoxytol and ferumoxtran-10 are approval dextran coating- SPIONs by the FDA for MRI [17, 18]. For first time, in an article published in 2010, the use of SPIONs for MR imaging inflammation of the central nervous system has been reported [19]. Some of central nervous system (CNS) disease such as Alzheimer and Multiple Sclerosis (MS) are detectable by these contrast agents [20, 21].

Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that causes the loss of the myelin sheath and decreased ability to move in people between 20-40 years old [22-24]. In fact, some inflammatory lesions named as plaques were seen in the brain and spinal cord white matter which represents the destruction of the myelin sheath and axons damaged. The initiation and progression of the disease, environmental factors, genetic and nutritional may be effective. Recent studies have shown that people who breathe in the air containing heavy metals that are susceptible to this disease [25]. It seemed that toxin metals across the blood-brain barrier (BBB) by circulation and cause to damage. Some viral diseases can terminate MS attacks by demyelination. On the other word, immune cells such as lymphocytes B and T and macrophages penetrate central nervous system (CNS) and cause inflammatory relapses by destruction of myelin sheath [26]. This information was guided scientists to produce MS in animal models and studied about “autoimmunity” [19]. Also, Bauer et al in 19996 reported the role of macrophages in autoimmune disease of CNS [27].

In patients with MS, diagnosed by MRI can help in the prevention and progression of the disease. Because in these patients can be relied on MRI to detect lesions and diagnose the disease stages and disabilities by these lesions and determine the effectiveness of treatment [29]. In MS, MRI contrast agents should be biocompatible and also be able to create high-resolution images [26].

EXPERIMENTAL

This study is a systematic review article, search by keywords: Multiple Sclerosis, MRI in multiple sclerosis, Magnetic iron oxide nanoparticles in MRI, Magnetic nanoparticles for MRI in multiple sclerosis through the web site of PubMed, Sciencedirect, Google Scholar, Scoppus in the period 2000 to 2016 was conducted.

RESULTS AND DISCUSSION

MRI in Multiple Sclerosis

The first application of MRI technique was returned to 1970s and 10 years later, this technique came to market [30]. The first application of MRI in MS diagnosis was reported by Young et al in 1981[31]. Imaging of the central nervous system can help in the diagnosis and treatment of diseases and functional changes in the brain and spinal cord. Imaging of brain and spinal cord with magnetic resonance imaging (MRI techniques) can approve the success of treatment [32]. The contrast agents should be able to cross the blood-brain and blood–cerebrospinal fluid (CFS) barrier in this disease [33]. Studies in animal models can be generalized to humans. So that encephalomyelitis (EAE) is animal model used in the study of multiple sclerosis in human. MRI (and T2 weighted imaging) is a powerful technique to determining the disease course and effectiveness of treatments in MS [34]. With hyper intensities on T2 w MRI resulting from white matter[35], cerebral grey matter and cerebellum [36] good results can be achieved for the detection and effective treatment of multiple sclerosis. T2 lesions in white matter can be observed since the onset of the disease until the disease progression, because the T2 contrast is not observed in healthy subjects. By MRI, Tedeschi et al studied gray matter atrophy and lesions in 597 MS patients and 104 subjects. They investigated both relapsing-remitting and secondary progressive patients and said amount of atrophy in secondary progressive patients is higher than relapsing-remitting patients both in white and gray matter [37].

T1 and T2- weighted imaging in MRI can help to identify the disease processes such as inflammation, demyelination and axon loss [38] and so the stage of the disease, such as monophonic, relapsing and remitting, primary or secondary progressive are recognized (Fig. 1).

In fact, studies suggests that MRI can help to observe lesions of brain and spinal cord at the start and during of MS attacks. These observations must be repeated three month later to identify progression of disease. In these observations, both T1 and T2-weighted MRI must be attended.

Also, Nathoo et al used MRI for testing drugs in MS [39]. Studies in MS patients using T1-weighted MRI for the amount of axonal damages can be used to determine the stage of disease or transition from relapsing and remitting to secondary progressive MS.

Gadolinium- tetraazacyclododecane tetraacetic acid (Gd-DTPA) has been used as MRI contrast agent for years. Gd^{3+} is a positive contrast agent that reduces T1 relaxation time [10]. The low sensitivity of Gd- DTPA, short circulation time and renal excretion of its complex cause to limit its MRI application [40, 41]. By nanotechnology, scientist could have MR images with high sensitivity to observe brain lesions (Fig. 2). This technology provided access to clearer images with less concentration of the contrast agents. Thus, some new contrast agents such as liposome with Gd- chelates, Gd_2O_3, PEG- Gd_2O_3 [43], Superparamagnetic iron oxide nanoparticles, nanoparticles containing Mn and Gd^{3+}, Gf [44], VCAM-1 [45] and ICAM-1 [46] were investigated. Research showed that gadolinium and manganese are rather toxic and cannot predict the impairment or disability, strongly [47]. Gf, VCAM-1 and ICAM-1were reported in animal model studies, so that, Gf is more sensitive than Gd and easily passes the blood-brain barrier [48].

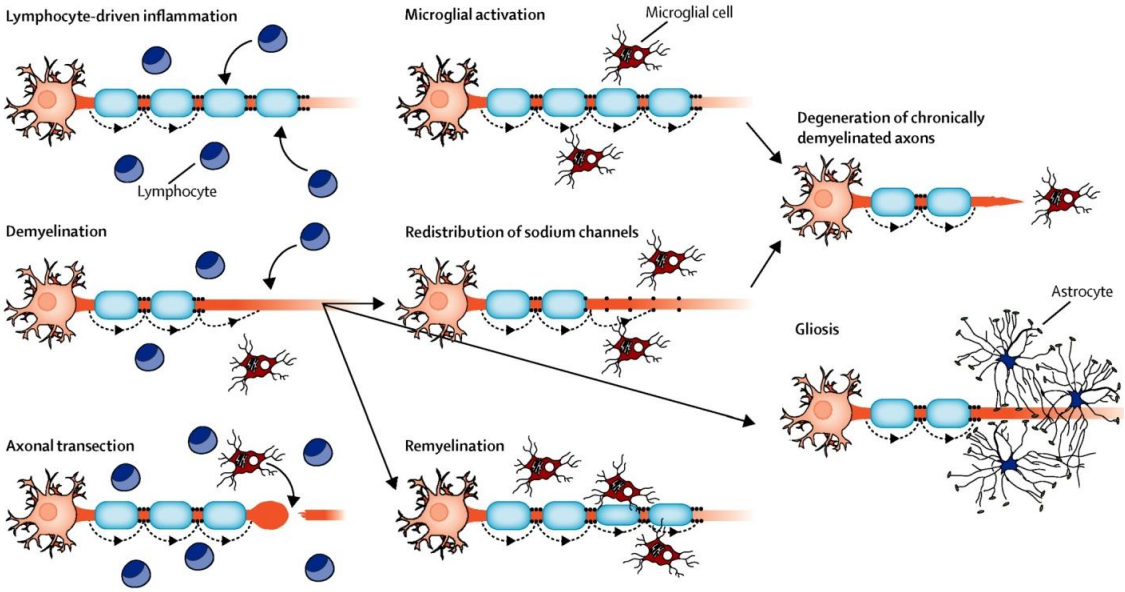

Fig. 1: Demyelination by inflammation and repair mechanism by microglial cells [28].

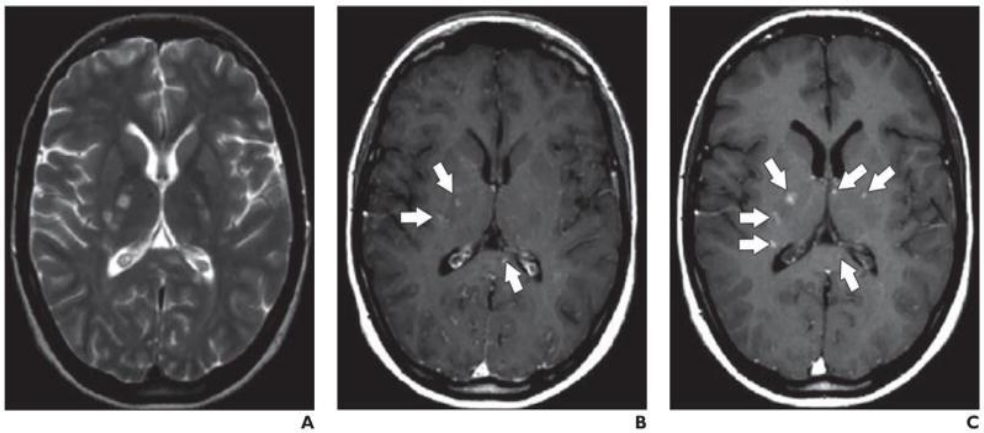

Fig. 2: Multiple sclerosis lesions. (Adapted and reprinted with permission from) [42].

Superparamagnetic iron oxide nanoparticles as MRI contrast agents

Iron oxide nanoparticles in size range 60-250 nm were called superparamagnetic iron oxide nanoparticles (SPIONs) because they magnetize in magnetic field and loss this property outside of external field [49]. This property cause using biocompatible iron oxide nanoparticles in medical applications such as MRI, drug delivery, hyperthermia [50]. Coating SPIONs with polymers (PVP, PEG, PVA, Dextran) help to prevent their aggregations and useful for medical applications due to avoid their toxic effects on the tissues [51-53]. Also, with these coatings, SPIONs show long blood circulation time due to the role of polymers to avoid absorption by proteins [54]. In blood half lives of SPIONs two factors are involved, The size and the surface charge [55, 56]. The particle size should be between 10-100 nm[13]. Particles with larger sizes are under attack by phagocytotic cells, while smaller particles are excreted from the kidney [51, 57]. Also, positive charge on SPIONs causes the nanoparticles stick to cells and reduces circulation time.

It is important iron oxide nanoparticles have uniform particle sizes, high magnetic moment, low toxicity and biocompatible coating for MRI application [58]. Some coatings that are clinical approved or in clinical test are: Dextran, Carboxydextran, Carboxymethyldextran, PEG-starch, Siloxane [59], Feridex(Ferumoxide)[60], Resovist (Ferucarbotran) [61]. Ferumoxytol (Feraheme) [62] and Ferumoxtran-10 are FDA approved SPIONs using in MRI[63].

SPIONs are negative contrast agents due to their effects on shortening water proton T2 relaxation times and produce darker and hyperintence areas in MRI. The lower toxicity than Gd-chelates, biocompatibility, superparamagnetism and coating with various shells result SPIONs to condidate good MRI contrast agents. The rate of relaxation, which can be expressed in the form r1(1/T1) and r2(1/T2), introduced the effectiveness of a contrast agent. The curve of r1 or r2 against iron concentration(C) expresses its effectiveness [64].Yazdani et al reported synthesis of SPIONs with SiO2 coating to use for MRI. They reported increasing Fe concentrations (0 to 0.16 Mm) cause to decrease T2 signals and increase 1/T2 (r2) [65].

In last tow decades, Scientists interested to use SPIONs in clinical fields. Ferumoxytol was the first FDA approval to use MRI [62]. Of course, some modifications on SPIONs are investigated in recent years. Lactoferrin, that is transferrin family, can conjugate to SPIONs and attacks to target brain cancer through penetrate the blood-brain barrier. By administration of Lf- SPION contrast agent and MRI studies with negative effects on T2 relaxation time, researchers of this work suggested good resolution diagnosis of Alzheimer's disease by Lf-SPIONs contrast agents [66].

Carboxymethyl chitosan-Acrylic Acid-Folic Acid (CMC-AA-FA) is another coating modification of iron oxide nanoparticles to use as contrast agent [67]. By comparing MRI imaging between uncoated and coated iron oxide nanoparticles on contrast of HeLa and NIH3T3 cells, Sahu and Co-workers investigated the CMC-AA-FA-IO are showed stronger contrast because of T2 relaxation time reducing. The ratio between IO and CMC was determined the size of nanoparticles. MTT assay was shown toxicity of iron oxide nanoparticles [67]. MRI investigation of superparamagnetic iron oxide nanoparticles modified by oleic acid and tween80 are studied by Wang et al in 2011. Intensity of T1 and T2 reduced and by dilution of concentration, intensity increasing of T1 was observed but T2 relaxation time was more reduced [68].

SPIONs can label stem cells to MRI studies. SiO2, citric acid, D- mannose, PVP, PLGA, PLMA, dextran, PAA, PEG and PEI are some of SPION coatings for this purpose [69]. Khurana et al reported the application of feromoxytol as a contrast agent for diagnosis of stem cells by IV injection up to 4 weeks after transplantation [70].

Sulek et al reported peptide functionalized SPIONs as MRI contrast agents by using amphiphilic lauric acid polymers (as peptide amphiphile) [2].This polymer causes the nanoparticles to be dissolved in water. Peptide functionalized superparamagnetic iron oxide nanoparticles as MRI contrast agents [2].

In clinical applications of SPIONs, there are numerous reports of their use in MR imaging of liver, bone marrow, lymph node, spleen, tumor and CNS. Gaglia et al used the SPION - enhanced MRI to study pancreas inflammation in type 1 diabetes mellitus patients [71].

SPIONs in Multiple Sclerosis Theragnosis

Application of SPIONs to the imaging of CNS inflammations was reported by Stoll and Bendszus in 2010 [19]. Experimental autoimmune encephalitis (EAE) is a animal model for studding

multiple sclerosis before that time [36, 72]. In inflammation, neutrophils and macrophages play an important role in fighting with infection agents and repair scars. In fact, the advantage of using SPIONs to gadolinium is phagocytosed by macrophages [56, 73, 74]. In fact, by application SPIONs for MRI we will be able assess CNS macrophage penetration but not with Gd [27]. SPIONs taken up by macrophages but not Gd-nanoparticles. This advantage makes them a better diagnosis agent for MRI [75]. SPIONs are able to across blood-brain barrier that is a barrier to penetrate unwanted substances to brain cells. This cause application drugs for delivering and treatment as well as diagnosis by SPIONs. In fact, by imaging of CNS in patients, doctors are able to diagnose and evaluate the destruction of the myelin sheath, and the lesions are measured by them. Due to the fact that damage the myelin sheath and axons on T2 can be verified in images, it is necessary to use SPIONs for having hyperintense imaging of lesions. For this goal, some recognition ligands could be attached to SPIONs to enhance MRI of inflammations (Fig. 3).

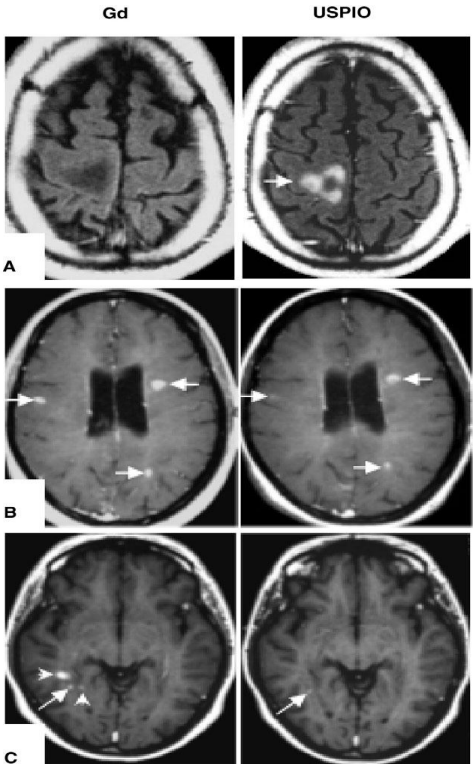

Fig. 3: MRI patterns of macrophage brain infiltration with ultrasmall superparamagnetic iron oxide particles (USPIO) (left panels) and blood-brain barrier (BBB) leakage with gadolinium-chelate (Gd) (right panels) in acute multiple sclerosis [76].

Of course, in ferumoxytol, Superparamagnetic properties cause using without labeling as a contrast agent. Until 2014, five FDA approved SPIONs were reported. Among them ferumoxytol and ferumoxides (feridex) were famous for multiple sclerosis treatment [61].

Autoimmune inflammation imaging in 14 multiple sclerosis (MS) patients by SPIONs was investigated by Vellinga and his group [12]. They detected total 188 lesions in these patients with SPIONs but only 44 lesions were detected with Gd contrast agent. In their research, the SHU555C agent was applied instead ferumoxtran-10. This contrast agent has shorter half-life than ferumoxtran-10. Tourdias et al assessed disease activity of MS with both SPIONs and Gd-enhanced in 24 patients with MS during 6 months [77].

This study was done during 3 years in 4 different hospitals both relapsing-remitting and progressive MS patients. They reported that more lesions seen with the use of nanoparticles and Gd than only Gd. It is noteworthy that SPIONs will not aggravate infections due to increasing iron contents after IV iron administration. The average daily iron requirements are 20-25mg/kg and the injection concentration is about 0.5 mg/kg [42]. Dousset et al in 2006 investigated about detecting macrophage, T cells and B cells infiltration in the brains of 10 MS patients. They compared their results with Gd contrast agent. Their study was on 33 acute lesions in these patients shown with ultra small iron oxide nanoparticles (USPIONs) and 31 lesions shown with Gd. They reported that USPIO give better macrophage activity information to Gd [77].

CONCLUSION

SPIONs are good candidate for MRI contrast agents in patients with multiple sclerosis. Some coated SPIONs approved by FDA for clinical application. Their biocompatibility, magnetic behavior, low toxicity and taking up by macrophages cause good resolution in brain MRI.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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