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Use of Manganese Supplement as an Alternative to Oral Contrast Agents for Gastrointestinal Tract Magnetic Resonance Imaging

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ABSTRACT

Introduction: This research aims to find an alternative oral contrast agents that can be used in magnetic resonance imaging (MRI) of the gastrointestinal (GI) tract, this contrast agent must be with no or minimum side effects and gives a best imaging quality.

Material and Methods: We have used manganese supplement (intake daily dose) after dissolving in different amounts of distilled water to obtain samples (the concentrations of the manganese solution) as oral contrast agents. The samples have been placed in tubes and imaged by MRI for finding the sample that has lowest concentration with best imaging sequences and contrast of the images. After that, this sample was tested by healthy volunteers. The subjects of the investigation were ten healthy volunteers who were scanned pre-contrast and post-contrast. The image result is measured by the signal value to calculate the SNR, contrast and then a different test is performed. There were significant variations in stomach SNR values between pre and post contrast ($p\text{-value} < 0.05$).

Results: The results show that the manganese supplement gives a good imaging sequences and contrast of the images. The contrast of manganese solution is positive on T1-weighted and negative on T2-weighted.This manganese supplement behavior is similar to the complex chemical manganese compounds studied in other investigations.

Conclusion: The manganese supplement can be considered as a positive contrast agent on T1-weighted and negative contrast agent on T2-weighted.

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Introduction

The use of MRI in gastrointestinal imaging has been difficult in distinguishing GI tract from intra-abdominal masses and normal organs. So the gadolinium-based solution (Gd) acts as a positive contrast agent while barium dilute (2%) acts as a negative contrast agent on T2 weighted these solutions have been used as oral contrast agents and can aid in this problem [1].

The gadolinium-based solution and barium dilute (like any other drug) can cause mild allergic reactions, flushing, nausea, rash, headache, etc. One of the most serious complications of the gadolinium-based solution contrast agent is nephrogenic systemic fibrosis [2], and they are expensive.

Therefore, many studies have been conducted to find alternatives to oral contrast agents, which are safer for patients and minimize the side effects of allergies to chemical contrast agents in MRI examination. The paramagnetic manganese compounds have been in the forefront of contrast agent research, as they are believed to be one of the most promising alternatives to gadolinium (III), such as the new manganese (II) complex [Mn(PyC$_3$A)(H$_2$O)] as the gadolinium alternative[3,4], MnO nanoparticles embedded in functional polymers as T1-contrast agent [5], macrocylic chelate [Mn(PC$_2$A-BP)][6], etc.

In addition, other researches have been conducted on organic materials that contain on manganese such as nature prepared fruit juices as pineapple juice [7], juice and pulp of acai fruit [8], medlar fruit, blueberry juice, green tea [9], jasmine tea [10] and black tea [11].

In this research, a new suggestion for using manganese supplement as an oral contrast agent for GI tract scanning in MRI. Because, the manganese supplement is safe on patients, available, and non-expensive compared to traditional contrast agents.

Basic equations

The magnetic resonance imaging is a type of scan, which uses strong magnetic field (B_o) and radio waves (RF) to produce detailed images (T1-weighted, T2-weighted, and proton density -weighted) from inside the body. A radio wave in a form of one or more short pulses is sent into human body, where it is absorbed by the nuclei of hydrogen atoms (^{1}H) [12].

The magnetic field (B_o) causes identical nuclei ^{1}H to precess at different Larmor frequency (f_L), which is determined by the Larmor equation

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$$f_L = \frac{\gamma}{2\pi} \cdot B_o \quad (1)$$

γ is called the gyromagnetic ratio, which is a property of a given nucleus[13]. *Gyromagnetic ratio* is also defined as the ratio between the magnetic moments(μ) to the total angular momentumI_N of the atomic nucleus [14].

$$\gamma = \frac{\mu}{I_N} \quad (2)$$

When an external magnetic field (B_o) is applied to the nuclei, these nuclei align either parallel or antiparallel with the magnetic field. The energy spacing ΔE_m between the parallel and antiparallel alignments is

$$\Delta E_m = \frac{\gamma\, h B_o}{2\pi} \quad (3)$$

Here h is the Planck constant [13]. To calculate the relative number of nuclei in each of the two alignments the Boltzmann equation can be used [15, 16]

$$\frac{N_{anti}}{N_{parallel}} = e^{-\frac{\Delta E_m}{KT}} = e^{-\frac{\gamma\, h\, B_o}{2\,\pi\, KT}} \quad (4)$$

Where k is Boltzmann's constant with a value of $1.38 * 10^{-23}\, J/K$, and T is the temperature measured in Kelvin.

Two kinds of spin measurements have the biological importance. One is associated with magnetic moments of unpaired electrons and the other with the magnetic moments of nuclei [17].

Materials and Methods

Some theoretical calculations were implemented by using the equations in section 2 to clarify the effects of nucleus and the unpaired electrons in the manganese atom on the signal of hydrogen atom in the water. Which contribute to the explanation of experimental results. As for the experimental study, its steps are summarized as follows

Oral contrast agent: We dissolved one tablet of manganese supplement (content 13.2mg of manganese citrate, or 4mg of manganese) (Pure Encapsulations) in each (120,240,360,480 ml) of distilled water to obtain four samples that have different concentrations and can be used as contrast agents. The four samples and distilled water have been tested by tubes for finding the sample that has lowest concentration with best quantitative image , after that, this sample was tested by healthy volunteer

Imaging samples in MRI: images of examinations were accomplished by 1.5Tesla-MRI machine(Siemens) and the imaging conditions are as follows :

- T1-weighted:- 2-dimentions, Gradient echo sequences, flip angle=65, repetition time=6.16mes ,echo time=2.15msec,
- T2-weighted:- 2-dimentions, turbo spin echo sequence, repetition time=2400msec, echo time=689msec, flip angle=140deg.

These sequences were used in vitro and vivo studies

In vivo study: ten healthy adult volunteers participated in the study (6 females and 4 males ranging in age from 23 to 47 years, with the average of age 33.6 years, and the average of body mass index 27.42 kg/m^2. The ten healthy volunteers were tested by two MRI examinations following an eight-hour fasting period; the imaging was done on them before and after three minutes drinking the best concentration of the manganese solution.

This study was performed at MRI unit, Imam Zain El Abidine hospital, Karbala-Iraq.

Results

Theoretical study

We did some theoretical calculations by equations from one to four in section 2 that show the impact of the nucleus and the unpaired electrons in the manganese atom in the magnetic field, as well as for the nucleus of the hydrogen in the water. This helps us to find out whether the electron or the nucleus changed the signal intensity of the hydrogen nucleus, as shown in the following table (1).

Table (1) shows that the energy spacing ΔE_m and Larmor frequency for the manganese nucleus are less than the corresponding values for the unpaired electron .The ratio $\frac{N_{anti}}{N_{parallel}}$ (2.5 per million) is very low, this means that the effect of the manganese nucleus is neglected in the magnetic field of 1.5T.

The energy spacing ΔE_m and Larmor frequency for the unpaired electron have the higher values in comparison the hydrogen nucleus, and the ratio $\frac{N_{anti}}{N_{parallel}}$ (99.3 percent) is relatively very high. Therefore, it can be concluded that unpaired electrons in the manganese atom cause change in the signal intensity of the hydrogen nucleus.

Experimental study

The four samples that have different concentrations have been tested by TDS meter to measure concentration of manganese content of water .as shown in table (2).

Table 1. Theoretical calculations under conditions, temperature=30°C, magnetic field (B) =1.5T

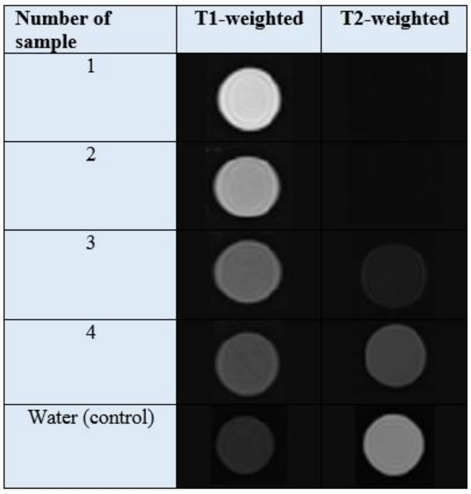
	Gyromagnetic Ratio γ ($Sec^{-1}.T^{-1}$)	f_L(Hertz)	ΔE_m(Joul)	$\frac{N_{anti}}{N_{parallel}}$
Hydrogen nucleus	2.6753×10^{8}	6.4309×10^{7}	4.2319×10^{-26}	1.0116×10^{-5}
electron	1.7587×10^{11}	4.2008×10^{10}	2.7820×10^{-23}	0.9934
Manganese nucleus	6.6156×10^{7}	1.5802×10^{7}	1.0465×10^{-26}	2.5015×10^{-6}

Table 2. Concentration of manganese in each sample

Number of sample	amount of water(ml) in sample +13.2mg of Manganese citrate	Manganese (ppm)
1	120	34
2	240	15
3	360	7
4	480	3

After that, the samples and water (control) were examined by tubes in MRI to obtain T1-weighted and T2-weighted at temperature=$30℃$ as shown in the figure (1).

Figure 1. T1-weighted (2-dimentions, Gradient echo sequences), and T2-weighted (2-dimentions, turbo spin echo sequence)



The section of optimal manganese concentration as oral contrast agent was carried out by scanning simples and measuring the signal intensity(S), standard deviation(SD), and calculating signal to noise (SNR) value.as shown in table(3)

The signal to noise (SNR) is the ratio of the average signal intensity (S_{av}) measured in the region of interest to standard deviation of the signal intensity in a region outside object being imaged. SNR is calculated to quantitative image assessment by the following formula [18]:

$$SNR = \frac{Average\ signal\ intensity\ (S_{av})}{Standard\ deviation\ (SD) of\ background} \quad (5)$$

From table (3), the sample (1) has highest signal intensity and SNR greater than one on T1-weighted, but on T2-weighted SNR is less than one so the signal becomes unusable. Therefore, sample (2) can be considered as the best to be as oral contrast agent and will be studied inside the human body.

We have evaluated the image quality in the magnetic resonance device through SNR and the contrast(C). The contrast (C) is a difference in signal intensity between two adjacent tissues or between contrast agent and surrounding tissues.

$$C = S_A - S_B \quad (6)$$

S_A, S_B are signals of two adjacent tissues or contrast agent and surrounding tissues[19].

The images information of ten volunteers was evaluated before and after the oral administration of the manganese supplement solution (sample 2). Measurements were performed to calculate signal intensities by drawing the area of anatomical (ROI) 300 mm^2 in the stomach area for each volunteer.

Data of ten volunteers were collected and tabulated for a two-group (before and after taking a manganese supplement solution). Version 22.0 of the SPSS (Statistical Package for Social Science) application was used to analyze the data. The estimations of the quantitative data were the mean and standard deviation (SD). For a two-group comparison, differences in attributes were examined using the t-test for quantitative data, The P-value < 0.05 on both sides was considered statistically significant, as shown table (4) and table (5)

Table 3. Values of signal intensity(S), standard deviation (SD), and signal to noise (SNR) of each sample on T1-weighted and T2-weighted. Where standard deviation (SD) of background= 1.14 on T1-weighted, and 0.56 on T2-weighted

Number of sample	T1-weighted			T2-weighted		
	S_{av}	SD	SNR	S_{av}	SD	SNR
1	490.44	8.17	430.21	0.15	0.39	0.27
2	350.90	6.94	307.81	0.69	0.27	1.23
3	204.28	4.95	179.19	35.44	1.20	63.29
4	139.95	4.47	122.76	124.31	4.70	221.98
water	88.41	3.37	77.55	454.78	9.41	812.11

Table 4. Signal intensity (SI), SNR, and contrast(C) in the stomach before and after taking a manganese supplement solution on T1-weighted

	The empty stomach	the stomach full of manganese solution	correlation	P-value
$SI_{mean} \pm SD$	96.18±2.804	536.81±2.5106	0.996	$1.94*10^{-26}$
$SNR_{mean} \pm SD$	79.59±4.204	443.99±13.896	0.958	$1.34*10^{-15}$
$C_{mean} \pm SD$	33.29±3.928	473.62±4.1667	0.925	$1.59*10^{-23}$

Table 5. Signal intensity (SI), SNR, and contrast(C) in the stomach before and after taking a manganese supplement solution on T2-weighted

	The empty stomach	the stomach full of manganese solution	correlation	P-value
$SI_{mean} \pm SD$	161.29±4.982	55.77±3.629	0.750	$4.49*10^{-15}$
$SNR_{mean} \pm SD$	61.56±9.548	26.40±1.007	0.861	$4.48*10^{-7}$
$C_{mean} \pm SD$	25.66±3.173	-369.67±1.1389	0.671	$3.14*10^{-21}$

Table (4) shows that the administration of a manganese supplement solution rises values of the signal intensity (SI), SNR, and contrast (C) in the stomach with a p-value $\ll 0.05$ (it is statistically high significant).

Table (5) illustrates that presence of manganese supplement solution reduces signal intensity (SI), SNR, and negative contrast (C) values in the stomach with a p-value $\ll 0.05$.

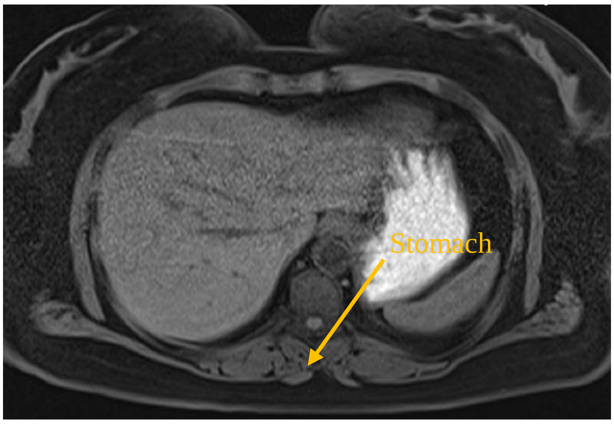


Figure 2. MRI transverse section of abdomen (T1-weighted) under imaging conditions 2-dimentions, Gradient echo sequences.

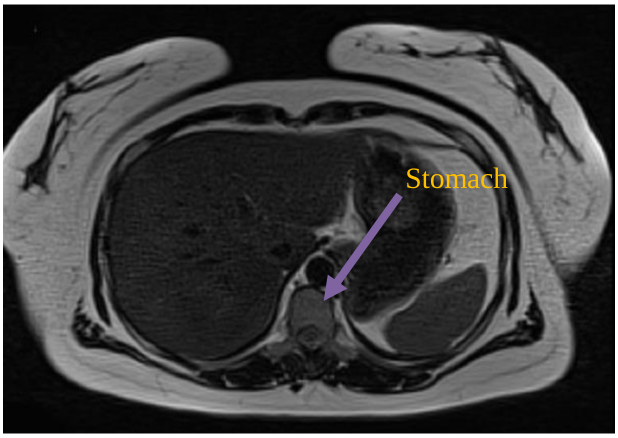


Figure 3. MRI transverse section of abdomen (T2-weighted) under imaging conditions**:** 2-dimentions, turbo spin echo sequence.

The contrast of manganese solution in the stomach is positive on T1-weighted and negative on T2-weighted. Therefore, it can be considered as positive contrast agent on T1-weighted and negative on T2-weighted

To clarify the behavior of the manganese solution in the human body: The healthy volunteer is 39 years old, and has a body mass index (BMI) =25.8kg/m^2, he drunk the solution (1 tablet of manganese supplement +240ml of water) after fasting for 8 hours. The volunteer has been examined after 3minutes after drinking solution, and the resulting MRI images as seen in figure (2) and figure (3).

Discussion

The manganese supplement solution was utilized as an oral contrast medium in this investigation because it possesses paramagnetic properties, namely it has a high magnetic susceptibility and is highly impacted by an external magnetic field. A safe daily intake of manganese was determined by the European Scientific Committee for Food (SCF) to be between 1 and 10 mg [21]. To make sure it is safe and has few adverse effects, one tablet of a manganese supplement (4mg of manganese) was used in this study. The solution (1 tablet of manganese supplement +240ml of water) gives a good quantitative image assessment; in addition to that, it is available and not expensive.

The oxidation state of manganese in manganese citrate($C_{12}H_{10}Mn_3O_{14}$) is two. Here, the electron configuration of manganese ion (Mn^{+2}) is $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 3d^5$[20]. Here, the manganese ion (Mn^{+2}) has five unpaired electrons. This explains the significant change in the signal intensity of hydrogen nucleus, despite the little concentrations of the manganese in water.

The Signal to Noise Ratio (SNR) is referred to as the ratio of the received signal to the average of the noise [18]. The intensity of stomach signal is assessed using SNR parameters in this study. A high gastric SNR indicates a strong signal in the stomach. The stomach SNR value increases before and after administration of a manganese supplement solution. There is a significant difference in the gaster contrast of the MRI images before and after the administration of a manganese supplement solution.

The presence of manganese in the water led to an increase in the signal intensity of the hydrogen nucleus on T1-weighted, and a reduction on T2-weighted. This behavior of manganese supplement is similar to the complex chemical manganese compounds in the other studies [3, 4, 6].

Conclusion

The manganese supplement is an effective alternative to oral contrast agents for gastrointestinal tract magnetic resonance imaging. Where it appears as good positive contrast agent on T1-weighted and a negative contrast agent on T2-weighted, it is also safe with no or minimum side effects and it is non-expensive compared to traditional contrast agents.

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