行政院國家科學委員會補助專題研究計畫成果報告

中藥磁石做爲 MRI 口服顯影劑的研製與臨床應用

計畫類別：☑ 個別型計畫　　□ 整合型計畫
計畫編號：NSC90－2314－B039－015
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計畫主持人：沈戊忠
共同主持人：陳中和
計畫參與人員：謝雲忠

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□國際合作研究計畫國外研究報告書一份

執行單位：中國醫藥學院 醫學系放射線學科

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一、中文摘要

本研究計劃以中藥磁石混合阻抗性澱粉含 xantham gum 及 gelose 50，製成口服懸浮液做爲磁振造影腹部檢查時，T2 顯影劑之用，以降低胃部及上腸胃道內液體的訊號來提高總膽管及胰管的變識率。

本計劃可分爲三大部分，第一爲體外試管試驗、第二爲動物試驗、第三爲人體試驗，在體外試管部分，我們以不同比率的磁石混合阻抗性澱粉，之後做各種脈衝波序的測試，找出最適合的濃度及能夠完全壓抑訊號，且不引起假影並不造成試管扭曲的濃度爲準。之後我們進行兔子的試驗，我們以 2 隻紐西蘭白兔做爲檢查對象，白兔在未喝磁石顯影劑以前先做一組影像，之後在以胃管抽乾胃內之分泌物，並灌入磁石溶液之後做另外一組影像，做爲比較，結果發現磁石溶液在胃部內的訊號，全部變黑而且胃的形狀完整沒有扭曲的現象；第三部分最後進行人體試驗，有 24 個病人接受試驗，在試驗前我們先給病人說明這磁石濃液的性質及其作用，之後先取得腹部磁振造影的各組影像含 T1、T2 矢狀及冠狀之切面影像，最後則給病人喝 300cc 到 500cc 的磁石溶液，再比較喝藥前及喝藥之後，胃部裡面訊號的變化，黏膜呈現的情況，及總膽管及胰管變識的程度等，在這 24 個病人有一些是接受 MRCP 檢查而來，有一些則是因爲肝臟腫瘤而來，有一些則是其他的病灶而來，比如胃部腫瘤而來，結果發現在 MRCP 的病人當喝了中藥磁石之後，胃內及十二指腸內液體的訊號很明顯受到完全的壓抑，而使總腸管的變識明顯的提高很多。

在三位胃部腫瘤的病人，喝了磁石濃液之後，可見腫瘤跟胃黏膜及胃局部的界限非常清楚的呈現，比未喝磁石顯影劑之前的影像要好，這一些病人在檢查進行之後，及幾個小時及一天之後，都接受當面或電話的訪談，追蹤其有無不適的症狀含腹痛、嘔吐或拉肚子的情況發生，結果沒有一個病人有上述的情況產生，有此研究計劃成果顯現，以中藥磁石混合阻抗性澱粉泡成的混合液是一既便宜安全，且可適用於日常腹部磁振造影檢查的顯影劑，可提高膽管及胰管的變識率，是值得開發的一種新產品。

關鍵詞：中藥磁石，阻抗性澱粉，動物試驗，T2 顯影劑，MRCP

Abstract:

This study aimed to develop a custom-made MR oral negative contrast agent by combination of and blending traditional Chinese medicine Magnetite with resistant starch xanthan gum and gelose 50. Thereafter, we test the feasibility of this new agent for signal suppression of upper gastrointestinal tract and its diagnostic value for magnetic resonance cholangiopancreatography (MRCP) and imaging of stomach tumor. The safety profile, palatability, compliance and complication were also evaluated.

This study was divided into three parts. They were in vitro study, animal study, and human study. At first, different amount of magnetite mixed with different ratio of xanthan gum and gelose was fully blended. After making sure no sedimentation, these suspensions were tested with different MR pulse sequences including in phase T1W gradient echo, multiple shots fast spin echo, and single shot fast spin echo. The echo time was up to around 1000 msec. Degree of signal suppression, artifact, and distortion of tube were evaluated. When having determined the optional concentration, two New Zealand white rabbits were examined. Both pre-contrast and post-contrast MR imaging with similar pulse sequences as above were undertaken. The degree of signal suppression and the contour distortion of the stomach were evaluated. The side effect of this mixture to the rabbits was also paid attention.

At last, we collected 24 patients who came for MR imaging of upper abdomen, including MRCP, MR of liver tumor and MR of stomach tumor. Both pre- and post-orally-enhanced images were acquired in both axial and coronal sections with different pulse sequences. The delineation of the stomach mucosa, artifact, and improvement for visualization of the common bile duct or pancreatic duct were evaluated.

Immediately, hours, and one day after ingestion of the contrast agent, the patients were asked and followed up for possible complications. The results showed this custom-made agent aided in delineation of stomach mucosa and increased the visualization of CBD and pancreatic duct. It has high potential role for clinical usage.

Keywords: negative contrast agent, magnetite, resistant starch, MRCP

二、緣由與目的

MR imaging of upper abdomen for evaluation of liver tumor, biliary system, pancreatic duct, and other lesions such as stomach tumors are now very popular in our daily practice. Its advantages include better image contrast, higher signal noise ratio, different imaging planes, and different pulse sequences for aiding diagnosis.

Magnetic resonance cholangiopancreatography (MRCP) has now become a standard diagnostic procedure for patients who were suspected of biliary or pancreatic diseases and ERCP was not suitable for them due to old age, potential complication, and exclusion of therapeutic procedures. MRCP is very simple to perform. Both thick slab and thin slices heavy T2WI (TE 180 –1000 msec) are acquired. The thin slices images can be reconstructed into three-dimensional image for better anatomic orientation.

The thick slab is, however, very fast to be acquired and needs only one or two seconds of imaging time. So it is very suitable for patients who are very weak and can not hold breath for up to 20 seconds. Although this image was very convenient for quick screening biliary and pancreatic condition, its main drawback is these is no possibility for reconstructed image. Therefore, once one segment of the ductal structure was not fully delineated or overlapped by other structures or signal, the diagnostic value was markedly decreased. From clinical experience, the main source of ductal obliteration comes from the overlapping high signal within the stomach and the duodenum.

How to get rid of these interfering signals becomes important. In recent years, there are already several commercial products for this purpose. These agents are, however, expensive.

In Taiwan, the limited budget in our current health insurance policy might restrict the popularity of this agent in our country. Therefore, we aimed to develop such kind of agent by ourselves and made it cheap, safe, simple to prepare, and very diagnostic.

For consideration of safety, we were quite confident about our self-made product. Because the three compositions including magnetite, xanthan gum, and gelose 50 are safe to intake. Magnetite is a traditional Chinese drug. Xanthan gum and gelose 50 are commonly used food additives and are non-absorbable. Our experimental results proved this new mixture is safe for both animal and human. No obvious complication or side effect was seen.

三、結果與討論

In Vitro Study

In vitro study was performed with magnetite amount ranged from 0.015gram to 0.1

gram/ 100 ml H2O and found 0.015 gram/100 ml H2O was optimal when mixed with adequate amount of xanthan gum and gelose 50 (Fig. 1). Under such concentration, the signal intensity of fluid was totally suppressed and the contour of the containing tube was not distorted. Other concentration, although also suppressed the signal intensity well, caused marked tube distortion.

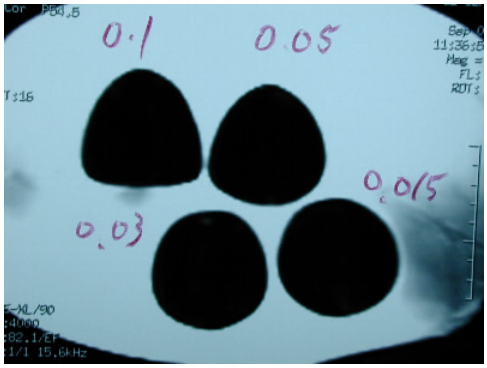

Fig. 1. Different concentration of magnetite were tested and the 0.015gram tube showed no evidence of tube distortion.

Animal Study

When conducting the experiment in three New Zealand white rabbits, we found the fluid signal in the stomach was totally turned to be dark as compared with the non-orally enhanced pulse sequences (Fig. 2). The contour of the stomach was also intact. There was no marked image artifact was seen. These rabbits were followed up for three days and no evidence of any side effect including vomiting, diarrhea was noted.

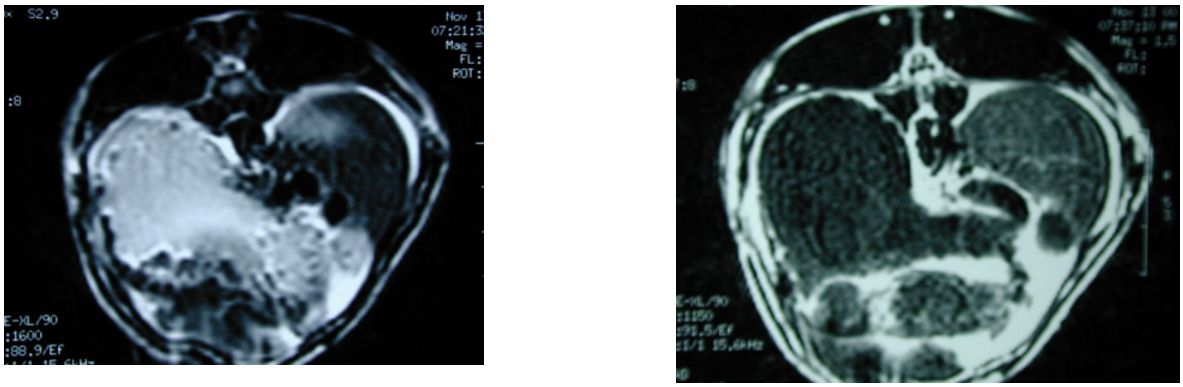

Fig. 2. The left side image was without oral contrast agent and the right side was with contrast agent. The signal intensity in the stomach was totally suppressed in the left side image.

Human Study

Totally twenty-four patients were included in this study. There were 12 males and 12 females. Age ranges from 2 years old to 85 years old. Fourteen patients came for MRCP examination due to suspicion of biliary or pancreatic problems. Seven patients were for studies of liver tumors. The rest three patients had stomach tumor.

Both axial and coronal sections of heavy T2WI were acquired for non-orally and orally-enhanced images. The signal intensity in the stomach of these 24 cases was completely suppressed and the mucosa was clearly delineated in enhanced images (Fig. 3). There was no artifact was identified. For three patients with stomach tumors, the interface of the tumor with the stomach mucosa was clearly seen (Fig. 4).

For MRCP studies, the orally-enhanced images showed totally or nearly totally suppressed signal in the stomach and/or duodenum. This made the identification of the common bile duct and pancreatic duct much easier in thick slab heavy T2WI (Fig. 5 & 6).

All patients were evaluated for the palatability of the contrast agent during the ingestion. And the possible complications including nausea, vomiting, abdominal pain, and diarrhea were evaluated immediately, hours, and one day after the ingestion of the contrast agent. All patients had no any complaint or side effects.

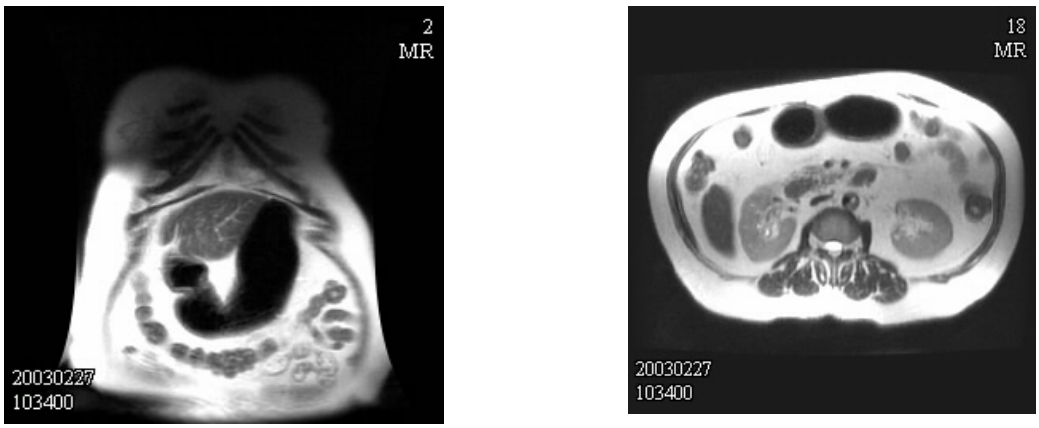

Fig. 3. Both coronal and axial sections showed the signal intensity within the stomach were totally suppressed and the mucosa was clearly delineated.

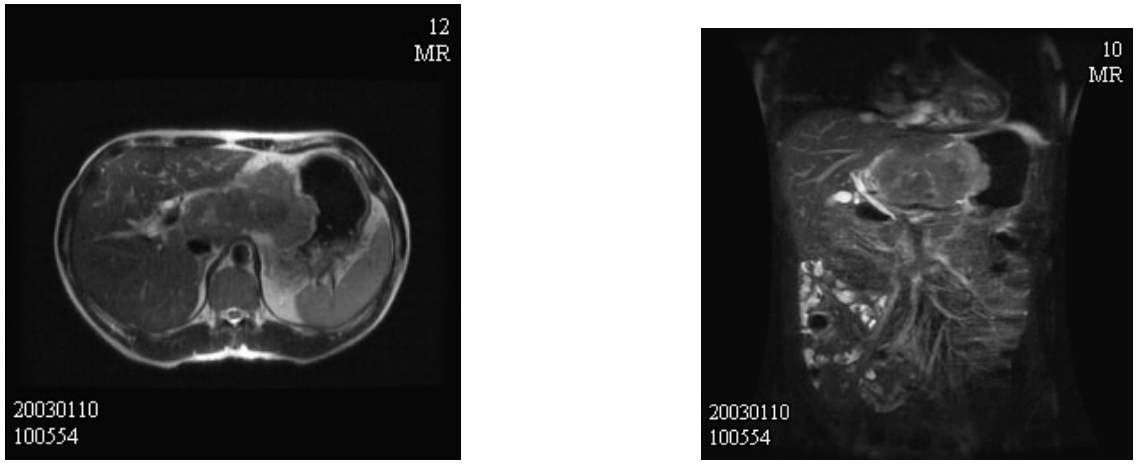

Fig. 4. Both axial and coronal sections of T2WI after ingestion of magnetite showed the tumor-mucosa interface was clear.

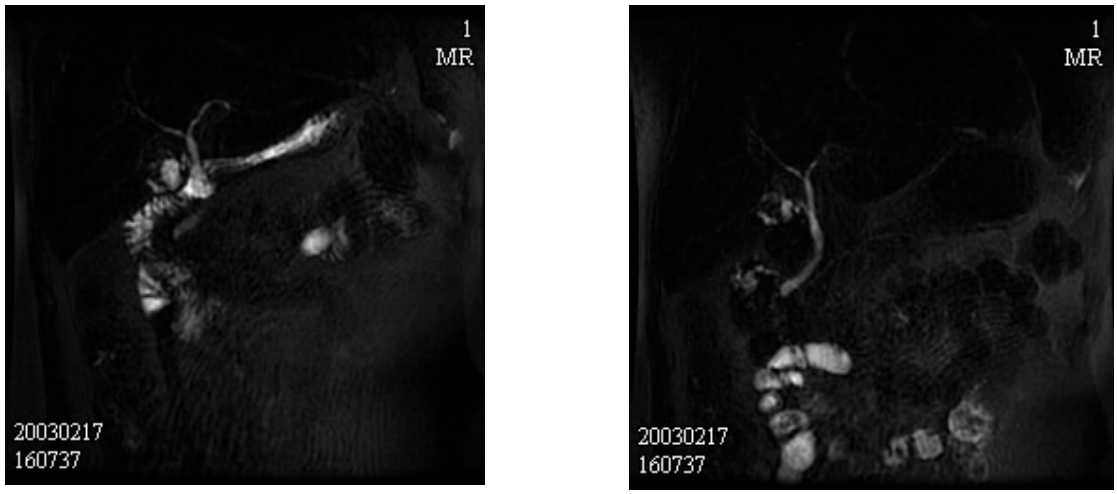

Fig. 5. After ingestion of magnetite suspension, the CBD in the right side image was more clearly identified than the non-enhanced image in the left side.

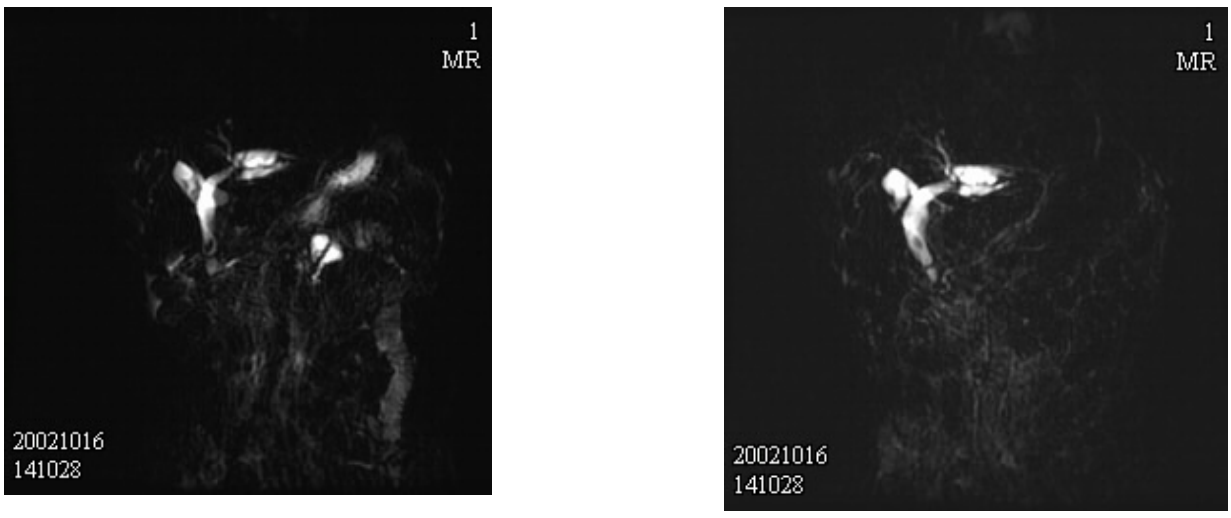

Fig. 6. After ingestion of magnetite suspension, the pancreatic duct in the right side image was more clearly identified than the non-enhanced image in the left side.

四、計畫成果自評

1. We have developed a self-made MR oral negative contrast agent by combination of traditional Chinese drug magnetite and resistant starch xanthan gum and gelose 50.
2. We have proved this new drug is cheap, simple to prepare, and safe for clinical usage.
3. We have evaluated the application of this new formula in aiding the diagnosis of upper abdominal MRI especially for MRCP and potentially for stomach tumor.

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