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Original article

The Effect of Contrast Agent on the Change of Hepatic Uptake of 99mTc-Mebrofenin in Patients with Liver Transplantation

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ABSTRACT

Purpose: 99mTc-mebrofenin hepatobiliary scintigraphy (HBS) is an important and clinically useful diagnostic imaging study for detecting complications after liver transplantation. CT contrast agents due to their high atomic numbers, lead to a decrease in gamma ray count rates. This study investigated the impact of CT contrast agents on the uptake of 99mTc-mebrofenin in the liver. **Materials and Methods:** The quantitative HBS was performed on sixty-two liver transplantation patients (male:female=36:26), with a mean age of 59.4±6.4 years. Statistical comparison of hepatic uptake reduction ratio (HURR%) before and after the injection of CT contrast agents was performed using a paired t-test. **Results:** Hepatic uptake of the reduction ratio was 94.47±3.65% for the pre-CT contrast agents and 92.17±4.00% for the post-CT contrast agents. HURR% after CT contrast agent injection showed a statistically significant difference compared to before the injection (t=11.09, P<0.001). **Conclusion:** It will be necessary to pay attention when examining the HBS of patients with liver transplantation after the injection of CT contrast medium. It is advisable to schedule the examination on a different day to prevent residual contrast medium in the body from interfering with the quantitative evaluation of the nuclear medicine examination.

Key Words CT contrast agents, Hepatobiliary scintigraphy, 99mTc-mebrofenin, Liver transportation, Hepatic uptake of reduction ratio

Introduction

Nuclear medicine is a medical specialty characterized by the use of radioactive materials called radiopharmaceuticals for diagnosis, therapy, and medical research. Nuclear medicine determines the cause of a medical problem based on organ or tissue function. In almost all diseases, physiological changes appear before anatomical changes. Therefore, they offer advantages in terms of early disease diagnosis and treatment evaluation.

Hepatobiliary Scintigraphy (HBS) is an essential diagnostic imaging study used in various clinical scenarios, including acute cholecystitis, chronic acalculous gallbladder disease, biliary obstruction, prediction of remnant liver function after partial hepatectomy and evaluation of complications after liver transplantation. Its strength lies in providing diagnostic information that defines pathophysiology rather than anatomy[1,2]. Biliary leaks following a liver transplant are uncommon but significant complications that can lead to post-operative morbidity. They can range from relatively high-flow leaks causing bilious ascites to low-flow ("trickle") leaks resulting in intra-abdominal collections[3].

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HBS is an important and clinically useful diagnostic imaging study for detecting complications after liver transplantation. The administered radiopharmaceutical of interest is 99mTc-mebrofenin (2,4,6 trimethyl-3-bromoiminodiacetic acid), which allows non-invasive examination of the hepatobiliary system. Among all IDA analogues, 99mTc-mebrofenin exhibits the highest hepatic uptake, minimal urinary excretion, and strong resistance to displacement by elevated serum bilirubin levels. It's almost exclusive uptake and excretion by the liver eliminate extrahepatic interference, making it the most suitable radiopharmaceutical for evaluating liver function[4].

Liver transplant patients are performed annual CT contrast examinations, nuclear medicine hepatobiliary scans and other tests to evaluate various parameters. These include the degree of increase in the gap between the bile ducts in the liver, blood flow in the hepatic artery, portal vein and hepatic vein. Additionally, these tests aim to detect abnormal signs in the spleen, pancreas and kidneys.

CT contrast agents cause a decrease in gamma ray attenuation and count rates due to their high atomic numbers. Thus, when gamma rays are attenuated by materials with high atomic numbers other than body tissues, image distortion occurs and affects quantitative test results[5]. Several studies have documented the impact of image quality degradation caused by interactions with contrast agents possessing high atomic numbers[5-10]. For example, Clare McKeown presented quantitative analysis showing that the contrast medium in positron emission tomography/computed tomography may cause significant artifacts. Pooyan Sahbae discussed “The Effect of Contrast Material on Radiation Dose at CT” and Eric C. Frey presented “The Accuracy and Precision of Radioactivity Quantification in Nuclear Medicine Images”[11-13].

The precise quantification of nuclear medicine scans has always been essential for early disease diagnosis and treatment evaluation. Therefore, we aim to evaluate the impact of residual contrast agents remaining in the liver parenchyma and excretion pathway on the gamma-ray count rate in nuclear medicine hepatobiliary examinations using 99mTc-mebrofenin, conducted following contrast-enhanced imaging tests for complication assessment.

Materials and Methods

1. Research subject

A retrospective review was undertaken of the 99mTc-mebrofenin hepatobiliary scintigraphy (HBS) performed from December 2013 to December. A total of 2,128 HBS performed, and 62 liver transplant patients (Male:Female=36:26, age 59.4±6.4 years old) who undergo annual examinations. To accurately evaluate the attenuation effect of the contrast medium, only patients who underwent hepatobiliary examination within 2 hours after contrast medium administration were included. The interval between tests was one year, and patients with no pathological changes were included.

2. Data acquisition

The patients were injected intravenously with 370 MBq of 99mTc-mebrofenin after a minimum fasting period of 3 hours. HBS images were acquired at 5 minutes and 90 minutes post-injection, obtaining 1000 kcounts in anterior views for each. All data were acquired on a gamma camera (Symbia E, Simens, USA) equipped with low-energy high-resolution (LEHR) collimators(Fig. 1). HBS images of the same patients were acquired during the 2 years following examination. The first year HBS images were obtained within 2 hours after injection of a CT contrast agent, and in the second year without injection of a CT contrast agent.

(A) Gamma camera (B) Acquisition method

Fig. 1. (A) The experiments were performed by using gamma camera (Symbia E, Simens, USA). (B) The hepatobiliary scintigraphy were acquired with injection in the first year and without contrast agent injection in the second year.

3. Hepatic uptake of reduction ratio (HURR%) Calculation

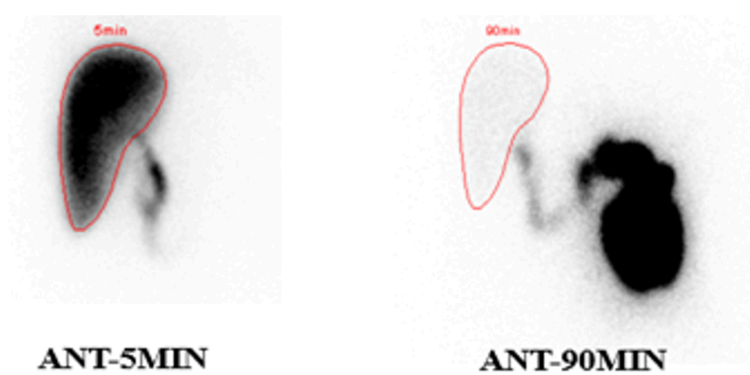
The hepatic uptake of reduction ratio (HURR%) was calculated using Siemens' image processing software[14]. A region of interest (ROI) was delineated on the liver parenchyma in the anterior views obtained at 5 minutes and 90 minutes(Fig. 2). Subsequently, the coefficient values within the ROI were computed by substituting them into the equation(Eq. 1).

$$HURR\% = \frac{(Liver\ ROI_{5\,\min} - Liver\ ROI_{90\,\min})}{Liver\ ROI_{5\,\min}} \times 100 \qquad \text{Eq. 1}$$

HURR% : Hepatic uptake of reduction ratio

Liver ROI5min : 5min image liver counts of ROI

Liver ROI90min : 90min image liver counts of ROI



(A) 5-minute full-scale images (B) 90-minute full-scale images

Fig. 2. The quantitative hepatobiliary scintigraphy with 99mTc-mebrofenin was performed on 62 liver transplant patients. A region of interest (ROI) was delineated on the liver parenchyma in the anterior views obtained at (A) 5-minute full-scale images and (B) 90-minute full-scale images. The hepatic uptake coefficient was calculated using the Siemens processing program.

4. Analysis

Statistical comparison between the hepatic uptake reduction ratio (HURR%) before and after the injection of CT contrast agents was conducted using a paired t-test. A P-value less than 0.05 is considered statistically significant.

Results

Hepatic uptake of the reduction ratio (HURR%) was 94.47±3.65% for the pre-CT contrast agents and 92.17±4.00% for the post-CT contrast agents(Fig. 3). HURR% after CT contrast agent injection showed a statistically significant difference compared to before the injection (Table 1).

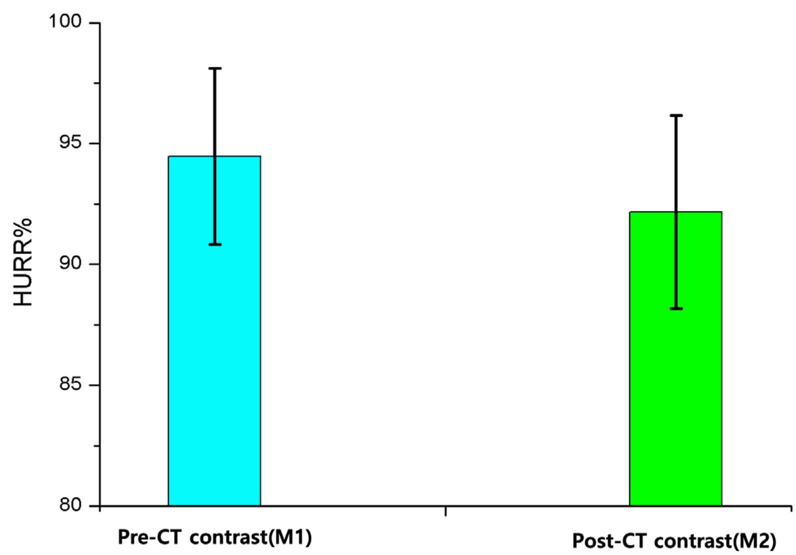


Fig. 3. The hepatic cell uptake coefficient was 94.47±3.65% in pre-CT contrast 92.17±4.00% in post-CT contrast.

Table 1. Comparison of hepatic uptake reduction ratio(HURR%) before and after CT agent administration using a paired sample t-test

	HURR% (M±SD)*	M. Difference	SE	t†	*P*	BCa‡ 95% CI	
						Lower	Upper
Pre-CT contrast(M1)	94.47±3.65	2.3	0.207	11.09	*P*<0.001	1.886	2.716
Post-CT contrast(M2)	92.17±4.00						

*HURR%(M±SD) : hepatic uptake of reduction ratio, M : mean, SD : standard deviation, SE : standard error, †t : (M1-M2)/(SD/√(n(sample size)), BCa : bias-corrected and accelerated, ‡ : bootstrap(sample size=10,000), CI : confidence interval

Discussion

Patients visiting the hospital undergo multiple tests on the same day of their visit for the diagnosis of diseases, confirmation of complications, and other assessments.

Nuclear medicine examination involves administering radiopharmaceuticals containing radioactive isotopes to the human body, followed by counting the radiation emitted from specific organs using equipment such as positron emission tomography (PET) and single photon emission computed tomography (SPECT). Nuclear medicine examination is highly valuable for non-invasively evaluating biological functions, although they often lack detailed anatomical information and have lower resolution due to biochemical and physical principles.

Radiological examinations often involve the injection of contrast agents with high atomic numbers to artificially increase the contrast of the image, enhancing the visibility of tissues or blood vessels through differential X-ray absorption of each tissue. If the contrast agent persists in the target organ during nuclear medicine examinations, it may affect the counting rate of gamma rays. During image acquisition, gamma rays emitted from the body interact with tissues, leading to absorption and scattering, which can make accurate quantification challenging. Also, attenuation caused by contrast agents and other materials with high atomic numbers can still induce image distortion, reduce spatial resolution, and affect gamma ray counting rates[15].

Papers related to gamma ray attenuation by contrast agents include Cha Sang-young et al.[6] highlighted the significant attenuation corrections in PET/CT due to the use of contrast agents. Another paper reported that over-attenuation correction by CT contrast agents affects quantitative evaluation standard uptake value (SUV), while Jin hyuk Lee[7] discovered that administering contrast agents at the technetium intake rate using a low-energy, high-resolution collimator resulted in decreased intake rates and increased noise in the test. Seong jae Pyo[5] also observed that higher contrast agent densities result in lower gamma ray counting rates in gamma cameras. Among papers, those conducted by Jinhyuk Lee[7] and Seongjae Pyo[5], specifically regarding the decrease in gamma ray counting rates due to contrast media, drew conclusions based on experiments using phantoms. The experiment using phantoms allow for controllable variables and are predictable. We conducted experiments to investigate how gamma ray counts are affected when nuclear medicine tests are performed on real patients immediately after contrast agent injection.

According to Korean clinical practice guidelines[8], the half-life of iodinated contrast medium is approximately 2 hours, and it takes about 20 hours to eliminate one dose of contrast medium in patients with normal renal function. While most of it is usually excreted through the urinary tract, a report by Joffe et al.[10] suggests that approximately 1% of water-soluble contrast medium is excreted through the liver in adults with normal renal function. The report suggests that when iodinated contrast agents are injected into the body in quantities exceeding 12.5g, they may be excreted into the biliary tract. In theory, if a nuclear medicine examination is conducted before the excretion of the contrast agent injected into the body, quantitative test of nuclear medicine using gamma rays emitted from the body are expected to be affected by the presence of residual contrast agent.

Among the papers discussing gamma-ray attenuation, Jeong Won-Jeong[16] reported that higher energy sources result in smaller attenuation coefficients, while higher density and atomic number of the medium lead to greater attenuation coefficients. This finding aligns with the author's observation that iodine contrast agents, with their high atomic number, attenuate gamma rays. This results in decreased coefficient values during nuclear medicine hepatobiliary tests conducted before the contrast agent is excreted into the hepatobiliary system. Young Jin Jeong[17] reported that even in CT imaging, low-energy X-rays in the range of 40-140 keV are significantly attenuated by contrast agents. This phenomenon is attributed to the similarity in energy levels between the X-rays used in CT imaging and technetium, which is the primary energy source utilized in nuclear medicine examinations, typically at around 140 keV. From a physics perspective, if a contrast agent with a high atomic number persists in the target organ during nuclear medicine examinations, it can be inferred that gamma-ray attenuation will be significant. Additionally, Ishii Shiro reported a case where the glomerular filtration rate temporarily decreased following a nuclear medicine DTPA test administered after the injection of an iodinated contrast agent[18]. This demonstrates the potential impact of contrast agents with high atomic number on nuclear medicine examination by attenuating gamma rays. Therefore, if iodine contrast agents are injected before nuclear medicine examination and remain in the target organ during the examination, they are expected to significantly impact the functional evaluation of nuclear medicine examination.

In this study, statistically significant results were obtained, indicating that performing nuclear medicine imaging within 2 hours before and after administering an iodine contrast agent resulted in a decrease in the coefficient value, affecting quantitative evaluation. However, this study's limitation lies in its exclusive use of anterior images for evaluation, neglecting to consider attenuation differences due to positional variations. In future research, obtaining data from posterior images and calculating the root mean square of differences in body positions would allow us to identify attenuation due to differences in bodily positions. It is speculated that with data from posterior images, a more accurate understanding of the influence of contrast agents on the gamma-ray attenuation coefficient could be achieved.

Conclusions

To investigate the potential impact of contrast agent remaining in the hepatobiliary duct on gamma ray count rates originating from the hepatobiliary tract, experiments were conducted. It was found that performing a hepatobiliary scan within approximately 2 hours after a CT contrast agent injection affects the gamma ray count rate. This decrease in count rate could be misinterpreted as a deterioration in liver cell function. Therefore, it is advisable to schedule a radiology test using an iodine contrast agent at a later time or on a different date before conducting a nuclear medicine examination.

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