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Sequential subtraction scintigraphy with ^{99m}Tc-RBC for the early detection of gastrointestinal bleeding

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To improve the early detectability of gastrointestinal (GI) bleeding, we have developed a new subtraction scintigraphic technique using *in vivo* labeled ^{99m}Tc red blood cells (RBC). Use of this new sequential subtraction method every 5 min makes it possible to detect early the bleeding site and calculate the bleeding rate. In phantom experiments, focal activity was detected on subtraction images at pump rates of more than 0.20 m*l*/min at any urethane thickness, but was negative on conventional scintigrams. The calculated pump rate by the subtraction method correlated well with the actual syringe pump rate ($y = 1.07x - 0.02$, $r = 0.99$, $p < 0.01$) in the case of an 8-cm urethane board as an abdominal wall. Twenty-four of 50 patients with suspected GI bleeding were confirmed to be positive within 24 hr. The subtraction method showed 15 true positive and 2 false positive cases within 60 min. On the other hand, the conventional scintigraphic method showed only 7 true positive and 1 false positive cases. Sensitivity of the subtraction method was 62.5%, which was significantly higher ($p < 0.05$) than that of the conventional scintigraphic method (29.2%).

These results suggest that sequential subtraction scintigraphy with ^{99m}Tc-RBC is an effective method for the early detection of GI bleeding and shortening the examination time as compared with conventional scintigraphy.

Key words: gastrointestinal bleeding, bleeding rate ^{99m}Tc-RBC, subtraction scintigraphy

INTRODUCTION

GASTROINTESTINAL (GI) bleeding sometimes poses a serious diagnostic challenge to physicians, especially when it occurs intermittently. Invasive techniques such as endoscopy and contrast angiography may provide accurate diagnoses, but have limitations in that they have to be performed during active hemorrhage. GI bleeding tends to be intermittent,[1] and therefore a study should be performed repeatedly over a period of 24 hr. ^{99m}Tc-labeled red blood cells (RBC) which remains in the intravascular blood pool for a prolonged period of time, is an ideal radiopharmaceutical for detecting the site of intermittent GI bleeding.[2–7] In the advanced aged group, the patient's condition is sometimes very serious, and therefore shortening the time of the study and enhancing the detectability of the bleeding site are important considerations.[8]

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We have developed a new noninvasive scintigraphic technique to quickly detect the bleeding site and calculate the bleeding rate by the sequential subtraction scintigraphy method and have compared results obtained with it to those of conventional scintigraphy. This technique is based on the following theoretical considerations.

THEORETICAL CONSIDERATIONS

When a radiopharmaceutical remaining in a vascular space is injected intravenously into a patient with active bleeding, blood activity gradually reaches a plateau in 10 min. The fraction of injected activity extravasated at the bleeding site gradually increases with the passage of time, but background activity is not significantly changed because of the relatively small amount of extravasated activity as compared to the total blood volume. This phenomenon is repeated each time blood recirculates, adding another fraction of the extravasate at the bleeding site. If scintigrams are taken every 5 min and are stored in a computer for 60 min, sequential 5 min subtraction scintigrams are easily produced by a digital gamma cam-

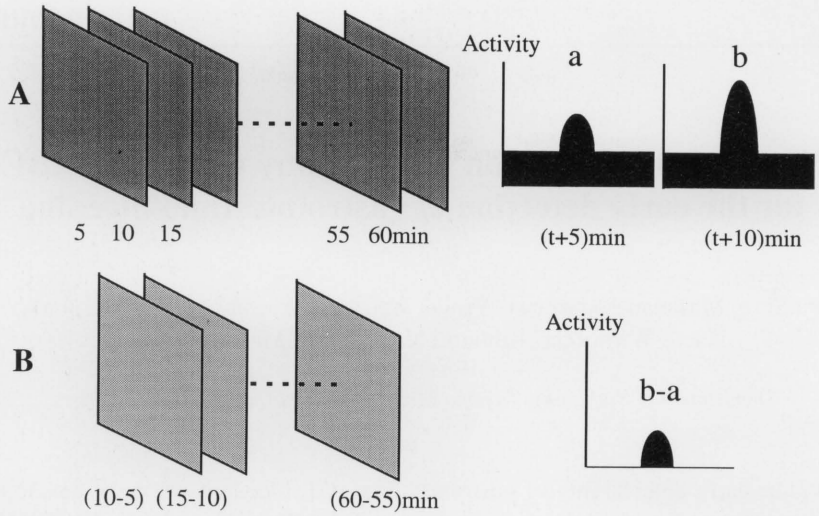

Fig. 1 Principle of sequential subtraction scintigraphy and calculation of bleeding rate. A: Conventional scintigrams, B: Subtraction scintigrams.

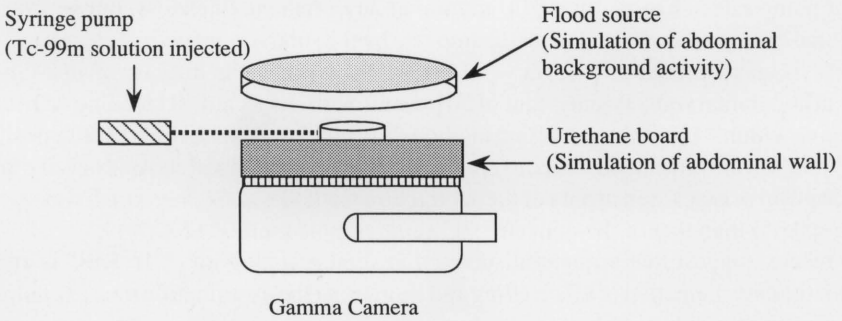

Fig. 2 A phantom simulating gastrointestinal bleeding on a gamma camera.

era. These subtraction scintigrams facilitate the early detection of the bleeding site as compared to conventional scintigrams because of the very low background activity and high contrast of the lesion to background (Fig. 1). Moreover, it is possible to calculate the bleeding rate, if the patient's blood sample is counted with the same camera correcting for the depth of the bleeding site. ^{99m}Tc-RBC is considered to be the most suitable agent for this purpose.

MATERIALS AND METHODS

Phantom experiments

As a simulation of GI bleeding, we used a syringe pump containing ^{99m}Tc-pertechnetate solution similar to the blood activity of a patient administered 740 MBq of ^{99m}Tc. Urethane boards of various thicknesses as abdominal walls and a flood source of ^{99m}Tc as abdominal background activity were used on a large-field-of-view gamma camera (Fig. 2).

Data were obtained in a 512×512 matrix at various rates of the syringe pump from 0.05 to 1.00 m*l*/min. Subtraction images were produced every 5 min at various pump rates at various urethane thicknesses. Detectable activity on the subtraction images was then assessed. Pump rates were calculated from the detectable activity per 5 min with correction for urethane thickness. The calculated rates were then compared to the actual syringe pump rates.

Clinical application

Fifty consecutive patients (26 men and 24 women) aged 5–93 years were studied. All patients referred with clinical evidence of GI bleeding as documented by anemia, melena and persistent maroon stool underwent ^{99m}Tc-RBC scintigraphic studies to localize sites of GI bleeding.

Radionuclide imaging was performed in the supine position with a large-field-of-view gamma camera interfaced with a computer. Energy was centered at 140 keV and a 20% window. Red blood cells were labeled *in vivo* by the method of Pavel et al.[9] A commercially available kit (Dai-ichi Radiopharmaceutical Laboratory Inc., Japan) containing 4 mg stannous chloride, and 20 mg sodium pyrophosphate was diluted with 3 m*l* of sterile saline and injected into an antecubital vein. Thirty min later, 740 MBq of ^{99m}Tc-pertechnetate as an adult dose was injected and then sequential images of the abdomen were taken at 5-min intervals for the first 60 min and then

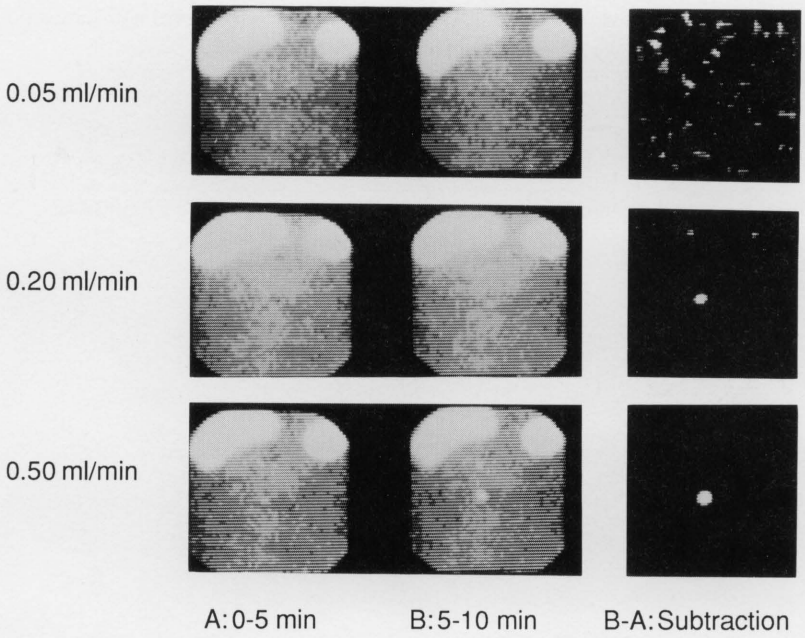

Fig. 3 Conventional and subtraction scintigrams of an abdominal phantom with continuous infusion of ^{99m}Tc solution by a syringe pump at the rate of 0.05, 0.20 and 0.50 ml/min. Focal activity was clearly seen on the subtraction images at pump rates more than 0.20 ml/min.

at 2–4 hr. Delayed images up to 24 hr were obtained when early images were negative and/or recurrent bleeding was suspected.

Data were obtained in a 512 × 512 matrix. Scintigrams were produced in a 256 × 256 matrix at 5-min intervals, and then 5-min images were subsequently subtracted from each other up to 60 min. Each 5-min image had more than 5,000 k counts. These sequential subtraction scintigrams with ^{99m}Tc-RBC were retrospectively interpreted by three nuclear physicians independently with regard to the detectability of a bleeding site and were compared to the results of conventional scintigrams within 60 min. The ^{99m}Tc-RBC scintigrams were considered positive if a focus of activity occurred corresponding to the location in the GI tract, which either increased in intensity or changed in location within the gut. Final diagnoses were established by endoscopy, angiography, operation and clinical findings such as persistent melena and maroon stool for 24 hr.

For statistical analysis, we used Student's t-test, and a p value less than 0.05 was considered to be significant.

RESULTS

Phantom experiments

Subtraction images were produced at various pump rates at various urethane thicknesses by means of phantom simulating active bleeding. Focal activity was detected on the subtraction images at pump rates more than 0.20 ml/min at any urethane thickness (Fig. 3). Pump rates were calculated from detectable focal activity per 5 min on the subtraction images at various urethane thicknesses and were compared with the actual syringe pump rates (Table 1). A pump rate more than 0.20 ml/min could be calculated at any urethane thickness. Good relationships be-

Table 1 Calculated pump rates by subtraction method in phantom experiments

Urethane thickness	Syringe pump rate (ml/min)				
	0.05	0.10	0.20	0.50	1.00
2 cm	N.A.	0.10	0.17	0.45	0.87
4 cm	N.A.	0.06	0.16	0.51	0.93
8 cm	N.A.	N.A.	0.25	0.51	0.93

N.A.: Not applicable due to non-visualization of activity

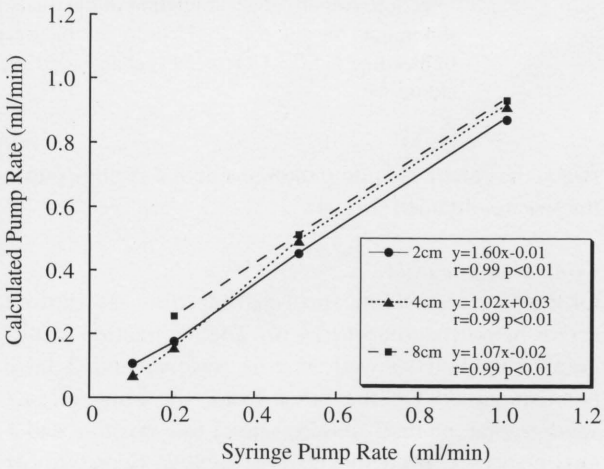

Fig. 4 Relationship between syringe pump rate and calculated pump rate by subtraction method at various urethane thicknesses.

Table 2 Comparison of detectability of GI bleeding between conventional non-subtraction method and subtraction method within 60 min*

Method	No. of true positive	No. of false positive	Sensitivity (%)	Specificity (%)
Conventional scintigraphy	7	1	29.2	96.2
Subtraction scintigraphy	15	2	62.5**	92.3

* Of 50 patients with suspected GI bleeding, 24 cases were established to be positive within 24 hr.
** $p < 0.05$

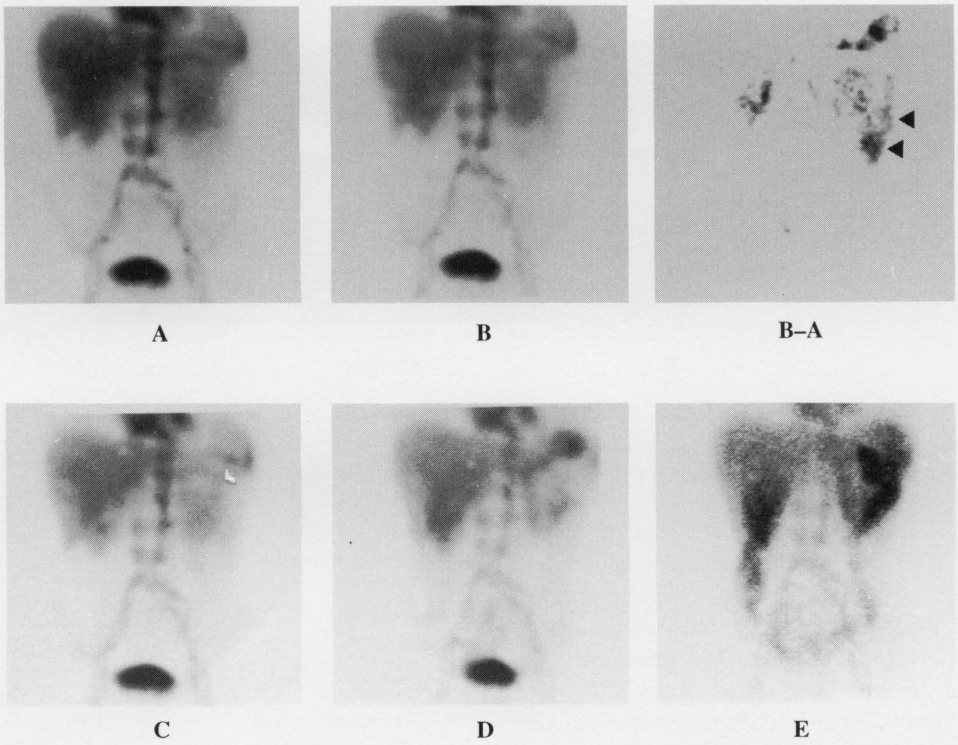

Fig. 5 A 79-year-old man with bleeding from small intestine due to metastatic cancer. Conventional abdominal scintigrams with ^{99m}Tc-RBC at 30 (A), 35 (B), 60 (C), 180 (D) min and 20 (E) hr after injection. Abnormal accumulation of the tracer is seen in the LUQ at 180 (D) min and more apparent throughout the colon at 20 (E) hr. A subtraction scintigram (B–A) by 35–30 min images shows the site of bleeding in the LUQ (arrows) at an early time. Free ^{99m}Tc-pertechnetate is observed in the region of stomach.

tween the calculated pump rates and actual syringe pump rates were obtained (Fig. 4).

Clinical application

Of the 50 patients with suspected bleeding, 24 showed active hemorrhage up to 24 hr. The subtraction scintigraphic method showed 15 true positive and 2 false positive cases. On the other hand, the conventional scintigraphic method showed only 7 true positive and 1 false positive cases within 60 min (Table 2). Sensitivity of the subtraction method was 62.5%, which was significantly higher ($p < 0.05$) than that of the conventional method (29.2%). No significant difference in specificity between the two methods was noted. The bleeding sites of 15 positive cases detected by the subtraction method were as follows; stomach 3, jejunum 7, ileum 1, ascending colon 2, and undetermined 2. As to the timing of positive scintigrams, eight of the 15 patients became positive at less than 30 min. The remaining patients became positive at less than 60 min. The earliest case was at 10 min in a patient with gastric bleeding. Representative cases are shown in Figures 5 and 6.

DISCUSSION

Endoscopy is usually the method of choice to determine a site of bleeding in the upper GI tract, but the procedure is difficult to perform in the small intestine and poorly prepared colon. Contrast angiography is of great use in both locating and controlling active bleeding from the GI tract. These procedures are, however, invasive and of limited use during active hemorrhage. In contrast, radionuclide techniques are noninvasive and can be used to follow up a patient with intermittent GI bleeding. The

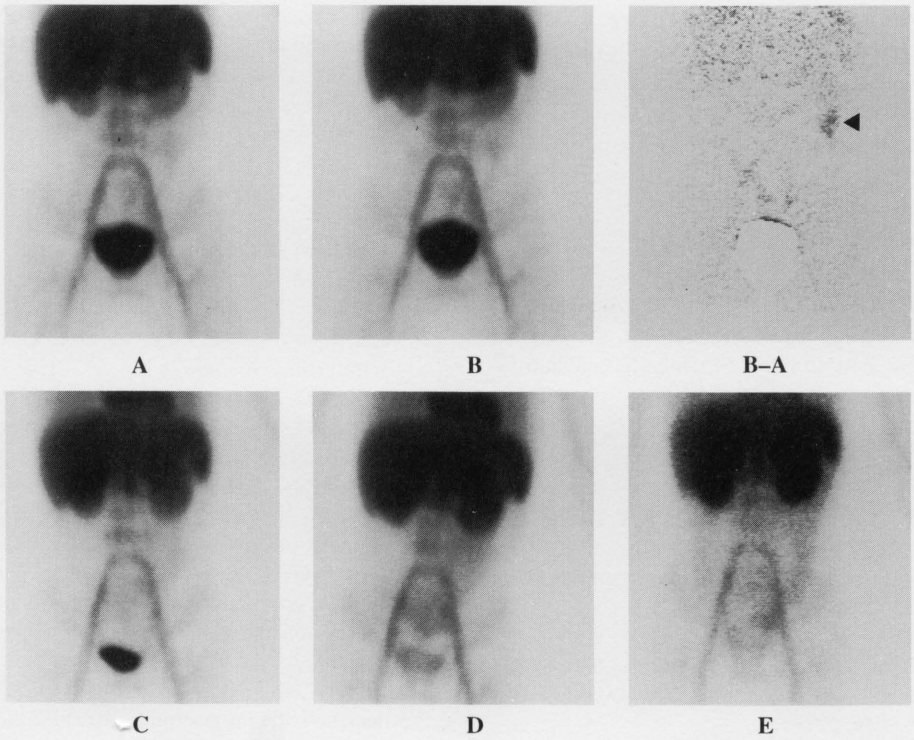

Fig. 6 A 7-year-old girl with bleeding from small intestine due to ulcer. Conventional scintigrams with ^{99m}Tc-RBC at 30 (A), 35 (B), 60 (C), 210 (D) min and 20 (E) hr after injection. Abnormal diffuse accumulation of the tracer is seen in the LUQ and mid abdomen at 210 (D) min and is mainly localized in the descending colon at 20 (E) hr. A focal area of intense activity in the LUQ (arrow) is clearly seen on a subtraction scintigram (B–A) by 35–30 min images corresponding to the site of bleeding from small intestine.

possibility of detecting bleeding sites with stable blood labeling agents was first suggested by animal studies with ^{51}Cr-labeled red blood cells and ^{131}I-labeled albumin.[10] Subsequently, ^{99m}Tc-labeled human serum albumin (HSA) was used to localize bleeding sites in patients.[11] At the present time, the use of HSA as the carrier is, however, largely abandoned owing to the superior binding of ^{99m}Tc with red blood cells and the problems caused by diffusion of circulating HSA into inflammatory and neoplastic lesions. Recently, ^{99m}Tc-sulfur colloids[12] and ^{99m}Tc-RBC[2–7] have been used for this purpose. ^{99m}Tc-sulfur colloids is rapidly cleared by the RES system and its half-life in blood is approximately 2.5–3.5 min.[13] A small amount of bleeding is therefore detectable because of the low background activity, but this procedure must be performed during active bleeding and is not suitable for intermittent bleeding.[5] On the other hand, ^{99m}Tc-RBC remains in the blood pool for a long time and is suitable for intermittent bleeding, although background activity is high and the minimum detectable bleeding is limited.[6,14]

In order to improve the high background activity and detectability of the minimum bleeding on ^{99m}Tc-RBC images, we have developed a new noninvasive scintigraphic technique, in which sequential subtraction scintigraphy enables us to detect a small amount of bleeding within 60 min because of the low background activity. In phantom experiments, subtraction scintigrams easily showed a focus of bleeding, despite negative conventional scintigrams (Fig. 3). The minimal detectable bleeding rate was 0.1–0.2 ml/min by the subtraction method (Table 1). This value was superior to the 0.20–0.40 ml/min reported by Chandeysson et al.[15] with conventional scintigraphy. In clinical application, we arbitrarily used the initial 60 min data for comparison because one large multiinstitutional study showed that a maximum of 80% of studies performed to detect bleeding of labeled red blood cells become positive within 60 min of the start of examinations.[5] The sensitivity of the subtraction method was 62.5%, which was significantly higher ($p < 0.05$) than that of the conventional scintigraphic method (29.2%). There were, however, 2 false positive cases, in which the subtraction method might produce artifacts due to the movement of the intestines. As to labeling red blood cells with ^{99m}Tc, we adopted an *in vivo* method.[9] This method yields more free ^{99m}Tc-pertechnetate than *in vitro* methods. Free ^{99m}Tc-pertechnetate might be another cause of false positive artifacts because of its secretion from the salivary glands and gastric mucosa, but another advantage of the subtraction method is the ability to calculate the bleeding rate every 5 min, as shown in Figure 3.

Our data from these experimental and clinical studies suggest that sequential subtraction scintigraphy with ^{99m}Tc-

RBC is an effective method for the early detection of GI bleeding as compared to conventional scintigraphy. Recent technical advances in digital gamma cameras enable us to make subtraction images easily in routine clinical practice and to shorten the examination time in pediatric and elderly patients.

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