

I. Neshandar Asli MD¹.
M.J. Ehsani MD².
H. Javadi MD³.

Colon Transit Scintigraphy by ⁶⁷Ga-citrate for Idiopathic Constipation

Background/Objective: Segmental colonic transit studies are important in patients with severe constipation. This study is the first Iranian preliminary survey of colonic transit scintigraphy using ⁶⁷Ga-citrate as a new method in constipated patients with normal radiographic and colonoscopic evaluations.

Patients and Methods: Thirteen patients with idiopathic constipation underwent colon transit scintigraphy. After oral administration of 6-7 MBq ⁶⁷Ga-citrate, serial abdominal images were taken up to 72 hours. Pattern classification was performed visually according to the distribution of radioactivity. Scintigraphic parameters such as geometric mean center (GMC) of segmental retention of tracer, as well as mean activity profiles and colonic tracer half-clearance time were calculated.

Results: Three patterns of colonic transit scintigraphy were recognized. Nine patients had the normal pattern, i.e. excellent propagation of activity. Three patients had the colonic inertia pattern with marked retention of activity in the transverse colon and splenic flexure at 48 hours. One patient had significant retention of activity in the rectosigmoid at 72 hours, defined as functional rectosigmoid obstruction (FRSO). No significant difference was seen in GMC24h between the normal pattern and colonic inertia (P=0.053), but GMC48h and GMC72h markedly differed between the two groups (P=0.016 and 0.025 respectively). The mean half clearance time (MCT) of the two groups was different (P=0.017). Our results are well compatible with scintigraphic diagnostic criteria in different patterns of colonic transit defined by other studies with different radiotracer.

Conclusion: Oral ⁶⁷Ga-citrate colon transit scintigraphy is a feasible method to evaluate idiopathic constipation and seems to be a suitable surrogate for radio-opaque markers.

KeyWords: oral ⁶⁷Ga-citrate, colonic transit study, idiopathic constipation, scintigraphy

Introduction

Constipation is a common clinical problem (incidence of 15% in the community), which is defined on the basis of symptoms of straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction, need for manual maneuvers to facilitate defecation, and two or less defecations per week, having an incidence.¹ It may be caused by various endocrine, metabolic, neurological and connective tissue disorders, and also medications.² The idiopathic form of constipation is more common in women and may be related to altered bowel motility caused by pelvic floor damage, anal sphincter dysfunction resulting in obstructive defecation, generalized slow bowel transit, abnormal gastro-colic reflex or the irritable bowel syndrome.³ Studies on patients with idiopathic constipation require reliable methods of measuring segmental colonic transit because several patterns of abnormal colonic motility have been observed including: the normal pattern, colonic inertia and functional rectosigmoid obstruction.⁴ The treatment of constipation can be decided on by determining the underlying abnormality in the segmental colonic motility.⁵ For

1. Associate professor, Department of Nuclear Medicine, Taleghani Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran.

2. Assistant professor, Department of Gastroenterology, Taleghani Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran.

3. Department of Nuclear Medicine, Taleghani Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran.

Corresponding Author:
Isa Neshandar Asli
Address: Department of Nuclear Medicine, Taleghani Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran.
Tel: 009821-22402995
Fax: 009821-22403694
E-mail: isa_neshandar@yahoo.com

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example in some patients with colonic inertia, assessment of the proximal colon by colonic transit scintigraphy may be helpful in deciding whether colonic resection would be appropriate⁶ and patients with FRSO may be treated with anal manometry biofeedback.⁷ And if surgery is contemplated, patients with colonic inertia will need a colectomy whereas patients with FRSO may need an anorectal myectomy.⁸

Early studies on colonic transit used markers such as dyes, seeds or even ball bearings, although they provided only crude data on oral-anal transit.⁹ Subsequent studies used radiopaque markers that could be followed by performing serial abdominal radiography^{3,9} which despite being more accurate than the earlier techniques, their measurement of segmental transit would require repeated radiographs.⁹ Also these techniques were not readily applicable to the colon for various reasons: (a) they are associated with a significant radiation burden; (b) artifactual errors may be introduced by the measuring systems; (c) the substances used for imaging (e.g., plastic pellets, and barium) may not be physiologic or may be large in volume; and (d) the start of the study has been poorly defined since the imaging agents are administered orally.

More recently, techniques using radionuclide studies are shown to provide accurate data on segmental colon transit and seem to be ideal for the study of colonic motility because of low radiation exposure, noninvasive imaging, subjective comfort and their feasibility for quantitative analysis.^{2,4-6} Earlier investigations involved invasive instillation of the tracer into the cecum¹⁰ and these were followed by studies using oral tracers such as ¹³¹I-labeled cellulose and then ¹¹¹In-DTPA, either absorbed onto polystyrene pellets or in solution.¹¹⁻¹³ All of these methods have

been shown to provide an accurate measurement of segmental colonic transit. However, indium is a relatively expensive isotope and not always readily available in Iran.

Recent studies showed that ⁶⁷Ga-citrate has a normal passage through colon without any prokinetic effect on the gut, its T1/2 =68 hours, given orally it is not absorbed from the bowel, and 98% or more of the ingested dose is excreted in the feces that makes it seem excellent for colon transit scintigraphy and a suitable surrogate for ¹¹¹In -DTPA.² In Iran, studies using radio-opaque markers are the most used protocols in constipated patients, while ⁶⁷Ga-citrate is readily available and less expensive; however, no previous Iranian study is available. The aim of this study was to assess different patterns of colonic transit on scintigraphy using ⁶⁷Ga-citrate, and comparing the results with other previous radionuclide studies.

Patients and Methods

Subjects and Data Acquisition

Patients with chronic constipation who were assumed to have idiopathic constipation based on history, physical examination, barium series, colonoscopy, and exclusion of other possible causes were referred for the nucleotide study by the project's consultant gastroenterologist. The patients had tried varieties of dietary options and medications for a long time.

For colonic transit scintigraphy with ⁶⁷Ga-citrate, the patients were asked to withhold medications for constipation 1 week before and throughout the scanning. The patients were allowed to maintain their normal diets. The study was not performed within 4 weeks following a colonoscopy, as the preparation for this procedure is frequently therapeutic.



Fig 1. Different pattern of scintigraphic colon transit study. (A) Normal pattern, there is acceptable propagation of activity through colon without segmental retention of activity during study. (B) Colonic inertia pattern, there is prominent retention of activity in transverse colon, Splenic flexure and rectosigmoid region at 48h and 72h, (C) Functional obstruction pattern, Significant retention of activity are seen in the elongated rectosigmoid region.

Table 1. Summary of GMC_i and MCT in patients

Diagnosis	N(f/m)	Age	Time of planar scintigraphy						MCT	
			24H		48H		72H		Hours	P Value
			GMC	P Value	GMC	P Value	GMC	P Value		
Normal (Group 1)	9(6/3)	38±12	4.76±1.40		6.56±0.38		6.77±0.17		31±11	
Inertia (Group 2)	3(2/1)	43±9	3.01±0.59	0.053	4.09±0.21	0.016	5.76±0.68	0.025	95±16	0.017
FRSO	1(m)	21	4.11		5.29		6.11		120	

tic in the short term. The patients were given an oral dose of ⁶⁷Ga-citrate (6-7 MBq) and they returned 6 hours after administration of the tracer, as well as in the mornings of three subsequent days. At each visit, subjects were placed supine under the medium energy parallel hole collimator, using the large field of view (LFOV) gamma camera (ADAC-SH Pegasys) with 20% window centered on the 92, 185 and 300 keV photopeak energy of gallium using a 128×128 matrix. The anterior and posterior views of the abdomen were obtained on a digital computer (SUN SOLARIS -SPARC) for 10 minutes. After all of the images were obtained, background subtraction was performed and the regions of interest (ROIs) were generated: the cecum and ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, rectosigmoid colon; and the activity of the excreted feces was calculated by subtracting the measured decay-corrected total colonic activity from the 6-hour count as the baseline total count. The decay-correction factor was determined using the following formula:

$$\text{Decay-correction factor} = \exp(-0.693 \times T / 78\text{h})$$

Which T is the study time in hours and 78 is the

half life of ⁶⁷Ga.¹⁰

Dosimetry

The critical organ is the lower large intestine which, in the constipated, receives 11.6 mSv for an 8 MBq of ⁶⁷Ga-citrate. Ovaries receive 2.8 mSv for the same dose.¹¹

Data Analysis:

The data from colonic scintigraphy was analyzed in four ways: direct observation, mean half-clearance time (MCT), time-activity profile and geometric center analysis (GMC).

Direct Observation: Serial scintigram were observed visually to note the patterns of radionuclide distribution. We divided scintigraphic findings in three groups: (a) the "normal" pattern, the activity arrived at the rectosigmoid on the second day as well as some excretion of the radiotracer was noted; (b) colonic inertia was identified as the slow transit throughout the colon during the study without significant segmental retention of the activity; and (c) functional rectosigmoid obstruction (FRSO) was defined as a holdup of the activity in the rectosigmoid region but normal transit in the rest of the colon.^{4,5,14,15}

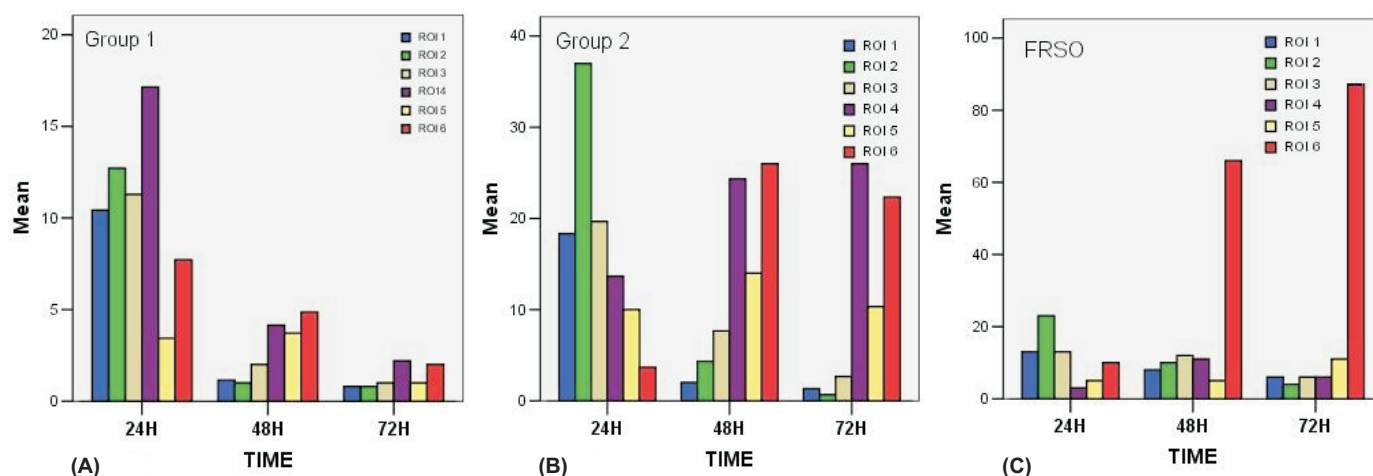


Fig 2. Activity retention profile in different patterns of colonic transit scintigraphy. (A) Group 1 with normal pattern colonic transit. (B) Group 2 with slow propagation of activity throughout colon. (C) A patient with prominent retention of activity in rectosigmoid.

(ROI 1=ascending colon, ROI 2= Hepatic flexure, ROI 3=Transverse colon, ROI 4= Splenic flexure, ROI 5= Descending colon, ROI 6=Rectosigmoid).

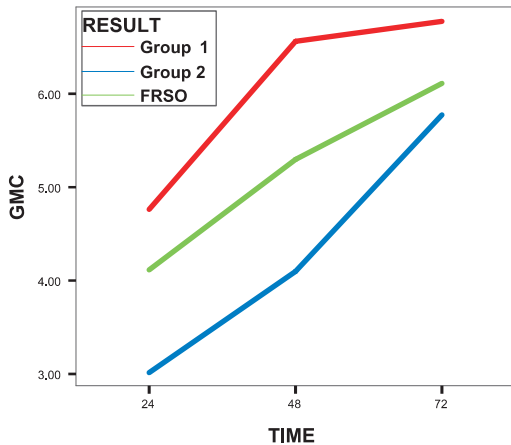


Fig 3. Curve of GMC_i in the three pattern of colonic transit scintigraphy. The greatest amount of GMC_{24h} and sharpness of initial slope are seen in patients with normal pattern, but in patients with colonic inertia, there is minimum deal of GMC_{24h}, but the greater sharpness of second slope. In patient with FRSO, there is acceptable GMC_{24h}.

MCT (Mean±SD): represent the time which half of the activity was eliminated from the colon.

Time-activity Profile: Using the data calculated for the time distribution, time-activity profile was obtained for each ROI. These graphs showed the percentage of the original bolus plotted as a function of time for each ROI.

GMC (Mean±SD): This technique used data from the time distribution analysis to generate a number that reflected the centroid of activity or overall progression of fecal material.^{16, 17} To determine the geometric center, each ROI was assigned a number: the cecum and ascending colon, 1; hepatic flexure, 2; transverse colon, 3; splenic flexure, 4; descending colon, 5; rectum and sigmoid colon, 6; and the calculated fecal activity, 7. To calculate the geometric center, the number of counts in a given region was divided by the number of total counts at 6 hours and multiplied by the region number. This calculation was performed for each ROI and the sum of the calculations represented the geometric center for a given time. The formula used to calculate the geometric center is:

$$\text{Geometric center} = \sum \text{ROI}_i \times i / \text{instilled counts}$$

Where *i* represents the ROI number, and ROI_{*i*} is the number of counts in ROI number *i*.¹⁰ The normal range of GMC_{*i*} are 2.0-7.0, 4.6-7.0 and 6.2-7 at 24 hours, 48 hours and 72 hours, respectively.⁴

For comparing GMC_{*i*} and MCT of different pat-

terns, the Mann-Whitney U test was performed.

Results

Thirteen patients (9 male and 4 female), aged 35±13 years (21- 53 years) were studied. Nine patients (6 male and 3 female) had the normal pattern of colonic transit with normal propagation of activity through out colon, and no abnormal segmental retention (group1). Three patients (2 male and 1 female) had a slow propagation of activity through colon defined as the colonic inertia (group 2). One patient had prominent retention of activity in rectosigmoid at 72 hours, defined as functional rectosigmoid obstruction (FRSO) (Figure 1).

Mean±SD of GMC_{24h}, GMC_{48h}, GMC_{72h} and MCT for group 1 were 4.76±1.40; 6.56±0.38, 6.77±0.17 and 31±11 hours, respectively (Table 1). Mean±SD GMC_{48h}, GMC_{72h} and MCT of group 2 were 3.01±0.59, 4.09±0.21, and 5.76±0.68 and 95±16 hours, respectively. The GMC_{48h}, GMC_{72h} and MCT of the patient with FRSO were 4.11, 5.29, 6.11 and 120 hours.

For comparing GMC_{*i*} and MCT of the groups 1 and 2, the Mann-Whitney U test was performed. There was no significant difference in GMC_{24h} between two groups (P=0.053), but the differences in their GMC_{48h} and GMC_{72h} were marked (P=0.016 and 0.027, respectively) due to slow propagation of activity in the right segments of colon during 24-48 hours. There was also a significant difference in the MCT of the groups 1 and 2 (P=0.017).

The time-activity profile of the percent retention of activity in different patterns of colonic transit is shown in Figure 2. Curves of the GMC_{*i*} are also shown in Figure 3.

Discussion

We found three patterns of colon transit on scintigraphy using ⁶⁷Ga-citrate, with each pattern having different GMC and MCT that are compatible with the previous colonic transit scintigraphic studies using ¹¹¹In-DTPA and ⁶⁷Ga-citrate.^{2, 4, 18} Normal values for GMC with ¹¹¹In-DTPA at 24 hours, 48 hours and 72 hours are 2.0-7.0, 4.6-7.0 and 6.2-7.0, respectively.¹⁶

Krevsky B et al.⁵ reported if GMC_{48h} was less than 4.6, a diagnosis of colonic inertia was made; never-

theless, if $GMC_{48h} \geq 4.6$ but $GMC_{72h} < 6.2$, the scintigraphic "diagnosis" was functional rectosigmoid obstruction (FRSO). Thus, our results on scintigraphic parameters are well compatible with the diagnostic criteria of colon transit study using ^{111}In -DTPA. Bartholomeusz et al.² demonstrated that the colonic transit study by ^{67}Ga -citrate was comparable with ^{111}In -DTPA and marker studies and results in the constipated subjects were significantly different from those of the controls. Mean half-clearance times for ^{67}Ga -citrate in the control subjects and constipated patients were 28.8 and 75.0 hours, respectively. For ^{111}In -DTPA they were 29.9 and 70.8 hours. They concluded that oral ^{67}Ga -citrate could be used as a safe alternative to ^{111}In -DTPA for accurate measurements of segmental colonic transit.²

Gallium has many of the properties of an ideal marker for transit studies. It is not absorbed from the colon when given orally, and its $T_{1/2} = 78$ hours compares well with the $T_{1/2}$ of indium (67 hours), allowing studies to be performed over several days. This is important because scanning may take as long as 5 days after ingestion of the tracer, particularly if delayed emptying of the descending colon or rectum is to be diagnosed correctly.

The method of analysis has varied from study to study. The simplest technique¹⁸ has been to assess the percentage retention in each colonic segment over time and to measure the clearance half-time of the entire colon. Others have also used simple time-activity curves involving individual colonic segments.¹⁹

A global measurement of transit is the geometric mean center of activity.^{10, 11} This indicates the average position of the tracer in the colon, with each position being weighted according to the amount of the tracer present at that site. We used GMC and clearance half-time method. The transit is slightly slower and more variable in females than males, but there is no slowing of transit with increasing age.¹³ In patients with slow transit constipation, there is abnormally high retention of activity in the right and left colons on all scans to 96 hours, while most patients with obstructed defecation demonstrated only abnormal retention in the rectosigmoid at 48 hours and by employing the GMC as an index of colon transit, most patients with the clinical slow-

transit constipation had early slowing of colonic transit at 48 hours while some only had late slowing at 72 and 96 hours.¹⁷ A number of studies have demonstrated faster transit of radio-opaque markers than the radio tracers in health, constipation and diarrhea.^{21, 22}

Colonic transit scintigraphy can alter the diagnosis in patients with chronic constipation. In a recent study that has examined the clinical utility of colon transit scintigraphy in the patients with chronic constipation, the referring specialists were asked about their diagnosis before and after the colon transit scintigraphy and the likelihood of the diagnosis. The diagnosis was changed after scanning in 37% of those considered to have slow-transit constipation, 43% of obstructed defecation and 64% of the irritable bowel syndrome. In addition, the likelihood of a particular diagnosis increased after scanning in many patients, allowing treatment to be instituted without further tests.²²

Several studies showed colon transit scintigraphy could be used to determine the efficacy of medications. Tegaserod, a 5-hydroxytryptamine₄ agonist, accelerated small bowel transit and had a small effect on colonic transit in patients with the constipation-predominant irritable bowel syndrome.²³ In constipated patients, after bisacodyl administration, a spectrum of abnormalities from slow transit involving the entire colon to slow transit involving only the rectosigmoid was seen.²⁴ Cisupride accelerated the right colon half-emptying time in both the colonic inertia and FRSO, significant only in the patients with colonic inertia.²⁵ Prucaloprid, a serotonin-4 receptor agonist, will improve symptomatology and decreased colonic transit time in patients with chronic constipations.²⁶

At present, there is a wide choice of tracers that can be used for studies of colonic transit (^{111}In -DTPA bound to resin pellets, liquid markers, etc.) but not all are available in Iran. However, ^{67}Ga -citrate is inexpensive, available, comfortable for patients and feasibly used for colon transit study. All our patients with idiopathic constipation had undergone radio-opaque marker studies that provided only crude data on the oral-anal transit. This study was the first experiment of colon transit scintigraphy in Iran to represent a new safe method easily applicable to the patients

with idiopathic constipation.

Limitation

This study is a preliminary investigation for introducing colon transit scintigraphy by ⁶⁷Ga-citrate. For determining its sensitivity, specificity and accuracy, further evaluation on an adequate sample and comparisons with the normal control group or radio-opaque markers is mandatory.

Conclusion

In summary, constipation is a common and often chronic disorder. Most patients have mild symptoms but a small number have severe symptoms that can be difficult to manage. Accurate measurement of segmental colon transit with an inexpensive, safe and reliable test is important in these patients. The use of ⁶⁷Ga-citrate reduces the cost and increases the availability of colonic transit studies. Gallium was well tolerated by all patients and radiation dosimetry was low and significantly less than the radio-opaque markers. In constipated patients, the dose can be reduced further by asking them to begin taking laxatives after completion of the tests to rapidly clear any retained tracer. Oral ⁶⁷Ga-citrate can provide quantifiable, objective data on segmental colonic transit in the patients with idiopathic constipation.

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