Accuracy of 99mTc (V)-Dimercaptosuccinic Acid Scintigraphy and Fecal Calprotectin Compared with Colonoscopy in Localizing Active Lesions in Inflammatory Bowel Disease

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ABSTRACT

INTRODUCTION

Due to limitation of colonoscopy in assessing the entire bowel and patients' intolerance in inflammatory bowel disease (IBD), in the current study, we aimed to prospectively compare the accuracy of 99mTc(V)-dimercaptosuccinic acid (DMSA) and fecal calprotectin with ileocolonoscopy as new methods for localizing inflammations.

METHODS

Current prospective study conducted between 2012 and 2014 on 30 patients with IBD attending Gastroenterology Clinic of Tehran University of Medical Sciences. Fecal calprotectin and disease activity were measured for all participants and all of them underwent 99mTc (V)-DMSA scintigraphy and colonoscopy. The accuracy of 99mTc (V)-DMSA scintigraphy and calprotectin in localizing bowel lesions were calculated.

RESULTS

A total of 22 patients with ulcerative colitis (UC) and 8 patients with Crohn's disease (CD) were evaluated in our study. Sensitivity, positive likelihood ratio (PLR), and positive predictive value (PPV) of scintigraphy and calprotectin over colonoscopy in localization of UC lesions were 86.36%, 0.86%, 100.00% and 90.91%, 0.91, and 100.00%, respectively. Meanwhile, it showed 66.67% sensitivity and 81.25% specificity with PLR=3.56, negative likelihood ratio (NLR)=0.41, PPV=84.21%, and negative predictive value (NPV)= 61.90% in localizing lesions in patients with CD. The calprotectin level had sensitivity, PLR, and PPV of 90.00%, 0.90, and 100.00% in detecting active disease over colonoscopy, respectively.

CONCLUSION

The 99mTc (V)-DMSA scintigraphy would be an accurate method for detecting active inflammation in follow-up of patients with IBD and assessing response to treatment as a non-invasive and complementary method beside colonoscopy for more accurate diagnosis of CD or UC.

KEYWORDS

99mTc (V)-DMSA scintigraphy; Inflammatory bowel disease; Clinical findings; Colonoscopy

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INTRODUCTION

Chronic inflammatory bowel disease (IBD) mainly has two subtypes; Crohn's disease (CD) and ulcerative colitis (UC). While UC mainly involves colon, CD can affect all sections of gastrointestinal tract. In

recent years, because of life style modifications, the incidence of IBD has increased.[1-5] Although IBD can have various clinical presentations, persistent or recurrent abdominal pain and diarrhea are the most common manifestations. Anemia, weight loss, and rectal bleeding are the other presentations.[6]

Currently, clinical, endoscopic, radiological, and biochemical investigations are combined for IBD diagnosis and follow up among which ileocolonoscopy with tissue sampling is the gold standard.[2,6-9] The best method for follow-up of patients with IBD is one of the most important challenges. On the one hand, patients with IBD require long-term monitoring because of the chronic nature of the disease and frequent flares and remissions.[10,11] On the other hand, endoscopy is not tolerated well by these patients due to difficulty of bowel preparation and occurrence of complications.[7,12-14]

Thus, other methods including fecal calprotectin level and scintigraphy have been developed to monitor the activity and severity of the disorder.[8,9] Measuring fecal calprotectin – calcium and zinc binding protein originating from inflammatory cells- by enzyme-linked immunosorbent assay methods (ELISA) is a sensitive marker for diagnosing intestinal inflammation and also has a good correlation with endoscopic and microscopic activity of the disease.[15-19] Likewise, scintigraphic imaging is also reliable in diagnosis and evaluation of disease activity as a non-invasive method especially when using radiolabeled leukocytes, which is more popular, because of higher sensitivity and specificity. However, the high cost and high dose of radiation are the main drawbacks of this method.[9,20-23]

Theoretically, low cost, high image quality, and easy preparation make pentavalent technetium-99m-dimercaptosuccinic acid (^{99m}Tc (V)-DMSA) an attractive practical method for investigating inflammatory processes; however, few studies have evaluated its efficacy in IBD.[23-25]

In the current study, we aimed to prospectively compare the sensitivity, specificity, and accuracy of ^{99m}Tc (V)-DMSA and fecal calprotectin with ileocolonoscopy for diagnosis of IBD and monitoring its activity.

MATERIALS AND METHODS

This single-center prospective study was approved by Ethics Committee of Tehran University of Medical Sciences (TUMS). Between 2012 and 2014, 30 participants were recruited from Gastroenterology Clinic of Imam Khomeini Hospital affiliated to TUMS.

Participants and study design

After obtaining informed consent, 30 symptomatic patients with IBD (21women and 9 men; range: 18-65 years) who were diagnosed by colonoscopy and biopsy sampling were enrolled. The initial diagnoses were UC and CD in 22 (16 women, 6 men) and eight (five women and three men) patients, respectively. Female patients who were pregnant and lactating were excluded from the study.

Then a standard investigation was performed, which included obtaining medical history, physical examination, measuring C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin followed by clinical assessment of disease activity by CD Activity Index (CDAI), Mayo score, and Harvey-Bradshaw index. The disease was considered clinically active in patients with CD if CDAI scores were higher than 150.

Then, all the cases underwent further diagnostic evaluations as well as ^{99m}Tc (V)-DMSA scintigraphy and colonoscopy. Each test was interpreted regardless of findings in the other test.

During the diagnostic assessments, the patients' pharmacological treatments were not subject to any change.

Reference study

The reference investigation was colonoscopy by a brand colonoscope (Olympus 190-series,USA) in which an experienced endoscopist blind to the results of the scintigraphy evaluated the colon following the standard preparation protocol (colonic cleansing with 4 L polyethylene glycol plus low-fiber diet 3 days before investigation).

The inflammatory lesions at endoscopy were evaluated based on the scale of 0-3 described by Gomes and colleagues.[26] In this scale, 0, 1, 2, and 3 stand

for normal, presence of mild inflammation with loss of vascular pattern, severe inflammation with contact bleeding, and more severe disease with friability, ulcers, or spontaneous bleeding, respectively.

99mTc (V)-DMSA Scintigraphy and Interpretation of Findings

All patients received intravenous injection of 20 microcuries of (740 MBq) 99mTc (V)-DMSA, which were prepared by a commercial (V)-DMSA kit (Parsisotope, Iran).

Starting at minute one, the scans were done in dynamic mode for 30 minutes. Subsequently, at 60, 120, and 180 minutes after the injection, the anterior planar projections of the abdomen and pelvis were attained, each for a10-minute duration. A gamma camera (E.cam, Siemens, Germany) equipped with a low-energy general-purpose collimator was used for scintigraphy. The radiotracer uptake distribution was recorded in each scan. Two nuclear medicine specialists unaware of the clinical diagnosis and endoscopic findings evaluated the scintigraphic data.

The bowel was divided into following five segments: rectosigmoid (RS), descending colon (DC), transverse colon (TC), ascending colon (AC), and small bowel. Any distinct center of uptake in any parts of the bowel on the scintigraphy was considered as a positive finding.

Same specialists assessed the severity of the disease by comparing the intensity of the uptake with the uptake in the iliac crest and scored it as following: score 0=no uptake, score1=uptakes less than iliac crest bone marrow, score 2=moderate uptake equivalent to iliac crest, and score 3=severe uptake greater than iliac crest.

The inter-observer variability was 81% with Kappa of 63% and then any disagreement was fixed by discussion. Finally, the scintigraphic results were compared with clinical data, fecal calprotectin levels, and endoscopic findings.

Statistical analysis

Descriptive statistics were performed for colonos-

copy, 99mTc (V)-DMSA scintigraphy, stool calprotectin level, and serum hemoglobin (Hb) level results. A comparison at the level of each different segment was derived between the lesions found at 99mTc (V)-DMSA scintigraphy, ileocolonoscopy, and calprotectin level by cross tab and Chi square test. Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), and negative predictive value (NPV) of 99mTc (V)-DMSA scintigraphy and calprotectin in localization of lesions of all segments were determined on a per-segment (for CD patients) and overall basis (for UC patients). Correlation between variables was determined by spearman or Pearson test. All the statistical analyses were performed using the SPSS software (version 18). p value < 0.05 was considered as statistically significant.

RESULTS

A total of 30 patients (22 [73.3%] patients with UC and 8 [26.7%] patients with CD) consisting of 19 men (63.3%) and 11 women (36.7%) were enrolled in our study and assessed by colonoscopy and 99mTc (V)-DMSA Scintigraphy.

Patients with UC:

The UC group included 16 (72.7%) men and 6 (27.3%) women. The median and mean disease duration was about 4 and 7.27±7.17 (1-23) years, respectively. The median calprotectin level was 1875.00 with a mean level of 1585.45±617.89 (0-2000), which was high in all but two patients. Median Mayo score was 9 with mean level of 9.40±2.32 (5-12), which demonstrated moderate to severe disease except in one patient with mayo score 5 that showed mild disease.

Median Hb level was 13.55(gr/dl) with mean level of 12.81±2.60 (5.70-16.70). 10 (45.5%) patients had normal level of Hb while 9 (40.9%) and 3 (13.6%) patients had mild and severe level of Hb, respectively. Hb level was correlated with Mayo score by Pearson's test with r =-0.381 and p value=0.08.

The result of Tc99 DMSA scintigraphy showed lesions in 19 (86.4%) segments while 3 (13.6%) segments did not have lesions. All the 19 positive segments were true. All 3 negative results were false negative. Gener-

Table 1: Sensitivity, Specificity, positive likelihood ratio (PLR) , Negative likelihood ratio (NLR) , Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of Technetium-99m (V) DMSA Scintigraphy in the Localization of Lesions, Calculated for Each Segment

Colonic segment	Sensitivity	Specificity	PLR	NLR	PPV	NPV
Total number of colonic segment N=240	66.67 (44.68-84.37)	81.25 (54.35-95.95)	3.56 (1.23-10.25)	0.41 (0.220.76)	84.21 (60.42-96.62)	61.90 (38.44-81.89)
Small intestine n=8	0 (0-84.19)	100 (54.07-100)	-	1	-	75% (34.91-96.81)
Descending colon n=8	83.33 (35.88-99.58)	100 (15.81-100)	-	0.17 (0.03-1.00)	100 (47.82-100)	66.67 (9.43-99.16)
Ascending colon n=8	71.43 (29.04-96.33)	0 (0-97.50)	0.71 (0.45-1.14)	-	83.33 (35.88-99.58)	-
Transverse colon n=8	33.33 (0.84-90.57)	60 (14.66-94.73)	0.83 (0.12-5.72)	1.11 (0.38-3.25)	33.33 (0.84-90.57)	60 (14.66-94.73)
Rectosigmoid n=8	83.33 (35.88-99.58)	100 (15.81-100)	-	0.17 (0.03-1.00)	100 (47.82-100)	66.67 (9.43-99.16)

ally, sensitivity , PLR, PPV, and Ҟ of Tc99 DMSA scintigraphy in localization of UC lesions were 86.36% (65.09%-97.09%) , 0.86 , 100.00% (82.35%-100.00%), and 0.78 (P<0.001), respectively. Correlation between Mayo score and calprotectin level with Spearman test showed r=0.43 and p value =0.042.

The sensitivity, PLR, PPV, and Ҟ of calprotectin level over colonoscopy were calculated to be 90.91% (70.84%-98.88%) , 0.91 , and 100.00% (83.16%-100.00%) in detecting the active disease, respectively . The aforementioned values were found to be 85.00% (62.11%-96.79%), 0.85, and 89.47% (66.86%-98.70%) for Tc99 DMSA scintigraphy over calprotectin in detection of active disease, respectively. Meanwhile, the Hb level was correlated with the Mayo score assessed by Pearson's test (r=-0.381, p value=0.08).

Patients with CD:

Patients with CD (three [37.5%] men, five [62.5%] women) had median disease duration of 3 years and mean duration of 7.62±8.79 (1-23) years. The median and mean calprotectin levels were 1840, and 1472.50±680.37 (0-1950), respectively. The levels were high in all patients but one. The median CDAI score was 277.80 with a mean level of 304.00±206.05 (57-730) reflecting severe disease in one (12.5%), moderate to severe disease in four (50%), asymptomatic remission in two (25%), and mild to moderate disease in one (12.5 %). The Harvey Bradshaw index showed a median of 6 with mean level of 9.12±11.48

(1-37), which showed active CD in six (75%) patients and clinical remission in two (25%) patients. Median Hb level of the patients were 11.85 with mean level of 11.98±3.50 (7.6-16.10) that showed normal level in four (50%), mild in one (12.5%), and severe level in three (37.5%) patients.

We performed per segment analysis for five regions (small intestine, ascending colon, descending colon, transverse colon and rectosigmoid), in eight patients with CD (table 1). The result of ^{99m}Tc (V)-DMSA scintigraphy showed lesions in 19 (47.5%) segments while 21 (52.5%) segments were reported negative. Among the 19 positive lesions 16 (84.21%) were true positive and 3(15.79%) were false positive. Amongst 21 negative results, 13 (61.90%) and 8 (30.10%) segments were true and false negative, respectively. Generally sensitivity, specificity, PLR, NLR, PPV, and NPV of ^{99m}Tc (V)-DMSA scintigraphy were 66.67% (44.68%-84.37%), 81.25% (54.35%-95.95%), 3.56 (1.23-10.25), 0.41(0.22-0.76), 84.21(60.42-96.62), and 61.90(38.44-81.89), respectively in localization of lesions in the five regions.

Even though the calprotectin level had sensitivity, PLR, and PPV of 90.00% (73.47%-97.89%) , 0.90 , and 100.00% (87.23%-100.00%) in detecting active disease over colonoscopy, respectively. The aforementioned values were 100% (59.04-100%) , 1 , and 87.50% (47.35%-99.68%) for Tc99 (V) DMSA scintigraphy over calprotectin in detection of active disease, respectively.

The Spearman's test showed a correlation between CDAI score and Harvey Bradshaw index with calprotec-

tin level (r=0.68, P value =0.06 and r=0.74 P value=0.03, respectively). The CDAI test was significantly correlated with AC uptake (*r*=0.73, *p* value=0.039) however its correlation with TC uptake (*r*=-0.071, *p* value=0.86) , DC uptake (*r*=0.43, *p* value=0.28) and RS uptake (*r*=0.61, *p* value=0.10) was not statistically significant. Besides, the correlation between Mayo score and [99m]Tc (V) DMSA scintigraphic score was not significant. Likewise the correlation between CDAI (*r*=-0.45, *p* value=0.26) and Harvey Bradshaw index (*r*=-0.68, *p* value= 0.06) with Hb level was not statistically significant.

DISCUSSION:

Different types of radionucleotide scintigraphy methods have been assessed for identifying inflammation in gastrointestinal tract. Although 67Ga is one of the primary techniques, it bears some restrictions including excretion to gastrointestinal tract and disguising the inflammatory zones and giving a false positive result. Meanwhile, long processing time of 67Ga makes it inappropriate for evaluating acute conditions. When it comes to human immunoglobulin, the accuracy of chemotactic peptides, labeled anti-granulocyte monoclonal antibodies, labeled anti-granulocyte monoclonal antibodies, simple colloids phagocytosed by leukocytes and labeled anti-E-selectin monoclonal antibodies , are impaired due to non-specific selectivity of their attachment to the inflammation zones and insufficient uptakes.[1,9,23,24,27]

Firstly in 1981 Yokoyama and colleagues introduced 99mTc (V)-DMSA 28 for diagnosis of malignant tumors and metastases. Later this method was applied for evaluating osteomyelitis, fractures, benign tumors, psoas muscle abscess, and bone and joint infections as well as inflammations.[23,24,29-33]

The higher accuracy of [99m]Tc (V)-DMSA scintigraphy (about 90%) and its capability for evaluating the whole bowel in association with no need to bowel preparation, non-invasiveness, cost effectiveness, and good diagnostic sensitivity (according to the results of our study and others) compared with the reported accuracy of 89% for colonoscopy and its limitation in assessment of the entire bowel, makes the former method an accurate device for assessing IBD activity.[1, 23,24]

Although leukocyte labeling and ^{99m}Tc hexamethyl-propyleneamine oxime white blood cell single photon emission computed tomographic imaging have been identified as methods for assessing disease activity in IBD, its recurrence in postoperative patients with CD, and response to treatment in IBD patients; prolonged processing time has prevented these methods to be used widely and studies are done to find simple, non-invasive, less costly methods.[24]

The results of our study showed high accuracy for [99m]Tc (V)-DMSA scintigraphy in assessing inflammation in IBD. We analyzed and compared the results of [99m]Tc (V)-DMSA scintigraphy and colonoscopy in CD and UC. The novelty of our study was to compare the accuracy of clinical, radiological, and colonoscopy methods for diagnosis of inflammation at the same time. In our study, a sensitivity of 86.36% and 85.00% was reported for [99m]Tc (V)-DMSA scintigraphy in detecting inflammation in UC patients over colonoscopy and calprotectin level, respectively. While, calprotectin level had 90.91% sensitivity in detecting inflammation compared with colonoscopy.

Moreover, the [99m]Tc (V)-DMSA scintigraphy had 66.67% sensitivity and 81.25% specificity compared with colonoscopy and 100% over calprotectin in active disease detection while calprotectin level was reported to have a sensitivity of 90.00% over colonoscopy. To recap, [99m]Tc (V)-DMSA is a potential radionucleotide scintigraphy for detecting and localizing bowel inflammations.[23]

In a study by Horsthuis and co-workers, different modalities for diagnosis of IBD were compared and per patients analysis scintigraphy demonstrated sensitivity and specificity of 87.8% and 84.5%, respectively. Likewise the mean per-bowel segment sensitivity and specificity were reported to be 77.3% and 90.3%, respectively.[2]

In a study by Lee and colleagues [23], in Taiwan on 62 cases suspicious of having intestinal inflammation , 15, 1, and 46 patients had final diagnosis of UC, CD, and miscellaneous colitis, respectively. Moreover 95% sensitivity and 94% specificity for detecting inflammation were reported for [99m]Tc (V)-DMSA scintigraphy.[23]

In another study by Koutroubakis [24], [99m]Tc (V)-DMSA scintigraphy was a useful method for identifying and localizing inflammation in intestine however it did not detect the distinct causes of inflammations.

In our study CDAI test was significantly correlated with AC uptake score of [99m]Tc (V)-DMSA scintigraphy; however its correlation with TC uptake score, DC uptake

score, and RS uptake score was not statistically significant. The correlation between Mayo score in patients with UC and 99mTc (V)-DMSA scintigraphic score was not significant in any of the regions. Though, in the study by Koutroubakis and co-workers [24] the correlation between 99mTc (V)-DMSA scintigraphic score and disease activity in patient with UC and CD were reported to be significant.

Among laboratory data, none of them were correlated with 99mTc (V)-DMSA scintigraphic score in patients with UC and CD, except for Hb levels that were correlated with DC uptake and RS uptake in patients with CD. In the study by Koutroubakis and colleagues 24 there was a significant correlation between C-reactive protein levels and the scintigraphic score.

They found high correlation between endoscopic and histological inflammatory activity and scintigraphic activity index. In assessing the extension of IBD, 99mTc (V)-DMSA scintigraphy was more accurate in patients with UC than CD. Furthermore, one of the limitations of this method is its incapability in identifying mild lesions in patients with CD. Another limitation would be the uptake by liver and bladder in the hepatic flexure. This problem could be resolved by taking the images in upright position with an empty bladder or with extra lateral views. An important limitation of our study was the lack of healthy control group that caused no negative results in standard test and we were unable to calculate specificity while comparing 99mTc (V)-DMSA scintigraphy with colonoscopy.

The results of the current study and reviewed literature suggest the idea that 99mTc (V)-DMSA scintigraphy would be an accurate method for detecting active inflammation in patients with IBD. It is not the perfect method for diagnosis of IBD; however it is a better choice for patients' follow-up and assessment of disease activity, response to treatment, along with the progression of disease. Similarly this method can be used in situations that colonoscopy is contraindicated or inappropriate or as a complementary method beside colonoscopy for more accurate diagnosis of CD or UC. However future studies are indispensable to compare this method with other diagnostic methods such as magnetic resonance enterography to find out a diagnostic method with better accuracy for diagnosis of patients with IBD.

CONFLICT OF INTEREST

The author declares no conflict of interest related to this work.

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