The potential role of radiolabeled red blood cell scintigraphy in diagnosis of endometriosis

Original Article

Maryam Shahbazi[1,2], Tahereh Poordast[3], Nahid Masoudi[1], Mahdi Haghighatafshar[1]

[1]Nuclear Medicine and Molecular Imaging Research Center, Namazi Teaching Hospital, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Student Research Committee, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Obstetrics and Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

(Received 27 May 2021, Revised 10 August 2021, Accepted 14 August 2021)

ABSTRACT

Introduction: Endometriosis is a gynecological disease and disorder that occurs when endometrial cells are shed through the fallopian tubes and are implanted on the surfaces of pelvis and abdomen. They form lesions that respond to hormones of the menstural cycle and will stimulate inflammation. It is controversial whether [^{99m}Tc]Tc-RBC scan would be sufficient for localizing bleeding sites. This study evaluated the value of [^{99m}Tc]Tc-RBC in diagnosing endometriosis.

Methods: Twenty patients were included in the study for endometriosis localization. Between the 2nd and the 5th days of menstruation, when the lesions were highly activated, [^{99m}Tc]Tc-RBC scan was performed and compared with TVUS, pelvic MRI and laparoscopic surgery findings. Scans of the patients were reported by two nuclear medicine specialists who were blind to patients' history.

Results: The patients' age range was 21-48 years (mean age: 35±8.79). The sensitivity, specificity, positive predictive value and negative predictive value for the right pelvic bleeding sites were 73.3%, 80.0%, 91.7% and 50%, respectively while the corresponding indices on the opposite pelvic site were find to be 87.5%, 75.0%, 93.0% and 60%, respectively.

Conclusion: Radiolabeled red blood cell scintigraphy has the potential to be used as an alternative procedure for diagnosing endometriosis.

Key words: Red blood cell; Scintigraphy; Endometriosis; Tc-99m

Iran J Nucl Med 2022;30(1):26-32
Published: January, 2022
http://irjnm.tums.ac.ir

Corresponding author: Dr. Mahdi Haghighatafshar, Nuclear Medicine and Molecular Imaging Research Center, Namazi Teaching Hospital, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: afsharm@sums.ac.ir

INTRODUCTION

Endometriosis (defined as the occurrence of uterine mucosa tissue in sites other than the uterus, mostly within pelvis) is known to be the most prevalent gynecological disease that affects 10% of women of reproductive age [1]. Despite many studies, the underlying mechanism for the development of this complex phenomenon is not fully understood [1, 2]. Clinical symptoms for endometriosis range from non-menstrual to menstrual dysmenorrhea. There is a controversy over diagnostic methods such as magnetic resonance imaging (MRI), transvaginal ultrasonography (TVUS), and laparoscopy. Although TVUS has been found to be the most accessible method to assess the ovarian [3] and bladder endometriosis [4], there is a controversy over its efficacy in case of deep pelvic endometriosis. Two studies have recommended rectal endoscopic sonography (RES) in combination with MRI can be beneficial for evaluating posterior pelvic endometriosis [5, 6]. Moreover, although Bazot et al. [7] identified TVUS as an accurate diagnostic method for intestinal and bladder endometriosis, but it failed to accurately diagnose uterosacral, vaginal and rectovaginal septum involvement.

On the other hand, MRI tends to have high sensitivity and specificity for the evaluation of deep pelvic endometriosis [5, 8-10]. However, a major pitfall that cause MRI to be challengeable is the bowel movement artifacts that make MRI, an inappropriate method in diagnosis of small superficial endometriosis [11]. Some researchers evaluated the serum CA-125 level in the diagnosis of endometriosis however, with limited diagnostic performance [2, 12]. Basically, increased CA-125 level is not specific for endometriosis and seems to have too low sensitivity to be a prognostic method for screening endometriosis [13]. Although laparoscopic surgery remains the most accurate method for visualization of endometriosis, in view of advancement of diagnostic imaging modalities, it is not routinely being utilized [14].

In another study, the accuracy of ^{99m}Tc labeled red blood cell ([^{99m}Tc]Tc-RBC) scintigraphy was assessed as a preoperative non-invasive imaging modality for the localization of endometriotic lesions [13]. They compared [^{99m}Tc]Tc-RBC results of 30 patients with established endometriosis with pelvic MRI findings; results determined the sensitivity and specificity of scintigraphy as 96% and 29%, respectively. The ability of [^{99m}Tc]Tc-RBC scintigraphy in differentiating fibrosis from active bleeding, which is an indicator of endometriosis, is an important consideration [15]. Despite the potential role this non-invasive modality for diagnosis of endometriosis, there are very few studies available in the literature [15-18]. The aim of this study was to assess [^{99m}Tc]Tc-RBC imaging for diagnosing endometriosis in comparison with laparoscopic surgery and pelvic MRI findings.

METHODS

Study population

Twenty patients who were candidate for laparoscopy to diagnose endometriosis were studied based on clinical, MRI and transvaginal sonography.

The study has been approved by the Ethics Committee (IR.SUMS.MED.REC.1396.115) and Institutional Review Board (Study Code No. 13217) of Shiraz University of Medical Sciences and informed consent forms were signed by all of the patients included in the study.

Procedure

Transvaginal sonography was performed with rectal prep for all patients then they were referred to the nuclear medicine department for [^{99m}Tc]Tc-RBC scintigraphy before performing laparoscopic surgery. Transvaginal sonography was performed maximum 4 month and MRI and [^{99m}Tc]Tc-RBC scintigraphy were performed maximum 2 month before laparoscopic surgery. Patients with history of claustrophobia, gastrointestinal bleeding or GI telangiectasia were excluded from the study. [^{99m}Tc]Tc-RBC scintigraphy was performed between the second to the fifth days of menstruation period.

After obtaining informed consent from the patients, 3-5cc whole blood was withdrawn and the labeling with Tc-99m was performed according to the instructions of a locally provided commercial RBC kit. The radiolabeled sample was then re-injected intravenously. Dynamic imaging of abdomen and pelvic was obtained (from xyphoid to pubis) for one hour, 60 frame/one-minute with a 256×256 size matrix and zoom factor based on patient size in anterior and posterior projections. Then the SPECT (Post void) images with dual head, large field of view gamma camera (GE) equipped with low energy all purpose (LEAP) collimators were obtained. The energy window was 20%, centered over 140 Kev photopeak of ^{99m}Tc. The patients were monitored over the entire course of the imaging for signs of adverse reaction. No side effect was noticed during the course of the procedure or afterward up to one week of observation.

Images were reviewed by two nuclear medicine specialists who were blinded to the patient's clinical status and related information. Marked abnormal uptake were considered as positive results.

The laparoscopy was performed for all patients. The results of [^{99m}Tc]Tc-RBC scintigraphy, MRI and ultrasound were compared with each as well as with laparoscopy in terms of diagnostic value, and the number and location of endometriosis lesion.

RESULTS

The mean age of patients was 35±8.79 (age range, 21-48) years. The efficacy of [^{99m}Tc]Tc-RBC, MRI and TVUS findings in comparison with histopathology results in the detection of right and left sided bleeding sites were evaluated. Radiolabeled RBC scintigraphy and TVUS results were available in 20 patients, and MRI results in 14 patients.

Tables 1 and 2 depict a comparison of scintigraphy, MRI, and TVUS findings with histopathological results on the right side. Although [^{99m}Tc]Tc-RBC scintigraphy showed similar sensitivity as TVUS findings (73.3%), the specificity of scintigraphy was found to be lower (80% vs. 100.0% respectively) as summarized in Table 1. The specificity of MRI (75.0%) was even lower than that of scintigraphy (80%). Additionally, following TVUS, predictive value of scintigraphy for positive subjects was 91.7%, followed by MRI (88.9%). Nevertheless, predictive strength of scintigraphy in terms of negative cases (50.0%) was the lowest in comparison with that of TVUS (55.6%) and MRI (60.0%).

As presented in Tables 2 and 3, sensitivity, positive as well as negative predictive values of scintigraphy in localization of left sided bleeding sites were higher than the right side. However, the specificity the opposite (75.0% for left vs. 80% for right side), with similar specificity as of TVUS. Surprisingly, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of both TVUS and MRI imaging in the detection of left sided bleeding sites were lower than the right side. Scintigraphy have had higher sensitivity (87.7%), specificity (75%), PPV (93.3%), and NPV (60%) on the left side in comparison with MRI (58.3%, 50.0%, 87.5%, and 16.7%, respectively) and TVUS (56.3%, 75.0%, 90.0%, and 30.0%, respectively).

Table 1: Comparison of scintigraphy, MRI, and TVUS findings with histopathologic results on the right side.

Imaging method	Image results	Pathology (+)	Pathology (-)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
[^{99m}Tc]Tc-RBC	Positive	11	1	73.3	80.0	91.7	50.0
	Negative	4	4				
TVUS	Positive	11	0	73.3	100.0	100.0	55.6
	Negative	4	5				
MRI	Positive	8	1	80.0	75.0	88.9	60.0
	Negative	2	3				

TVUS: Transvaginal ultrasonography, MRI: Magnetic resonance imaging, PPV: Positive predictive value, NPV: Negative predictive value

Table 2: The comparison between [^{99m}Tc]Tc-RBC scan, TVUS and MRI to diagnose endometriosis.

	[^{99m}Tc]Tc-RBC scan		TVUS		MRI	
	Right (%)	Left (%)	Right (%)	Left (%)	Right (%)	Left (%)
Sensitivity	73.3	87.5	73.3	56.3	80.0	58.3
Specificity	80.0	75.0	100.0	75.0	75.0	50.0
PPV	91.7	93.3	100.0	90.0	88.9	87.5
NPV	50.0	60.0	55.6	30.0	60.0	16.7

TVUS: Transvaginal ultrasonography, MRI: Magnetic resonance imaging, PPV: Positive predictive value, NPV: Negative predictive value

Table 3: Comparison of scintigraphy, MRI, and TVUS findings with histopathologic results on the left side.

Imaging method	Image results	Pathology (+)	Pathology (-)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
[^{99m}Tc]Tc-RBC	Positive	14	1	87.7	75.0	93.3	60.0
	Negative	2	3				
TVUS	Positive	9	1	56.3	75.0	90.0	30.0
	Negative	7	3				
MRI	Positive	7	1	58.3	50.0	87.5	16.7
	Negative	5	1				

TVUS: Transvaginal ultrasonography, MRI: Magnetic resonance imaging, PPV: Positive predictive value, NPV: Negative predictive value

Table 4: Comparison of biomarkers results with clinical parameters in patients with endometriosis.

	Biomarker		Clinical Parameters					
	CA125 (%)	AMH (%)	Dysmenorrhea (%)	Dyschezia (%)	Pelvic pain (%)	Dyspareunia (%)	Dysuria (%)	Infertility (%)
Sensitivity	73.7	73.3	94.7	52.6	68.4	57.9	52.6	78.9
Specificity	0	0	0	100	0	100	100	100
PPV	93.3	93.3	94.7	100	92.9	100	100	100
NPV	0	0	0	10	0	11.1	10	20

PPV: Positive predictive value, NPV: Negative predictive value

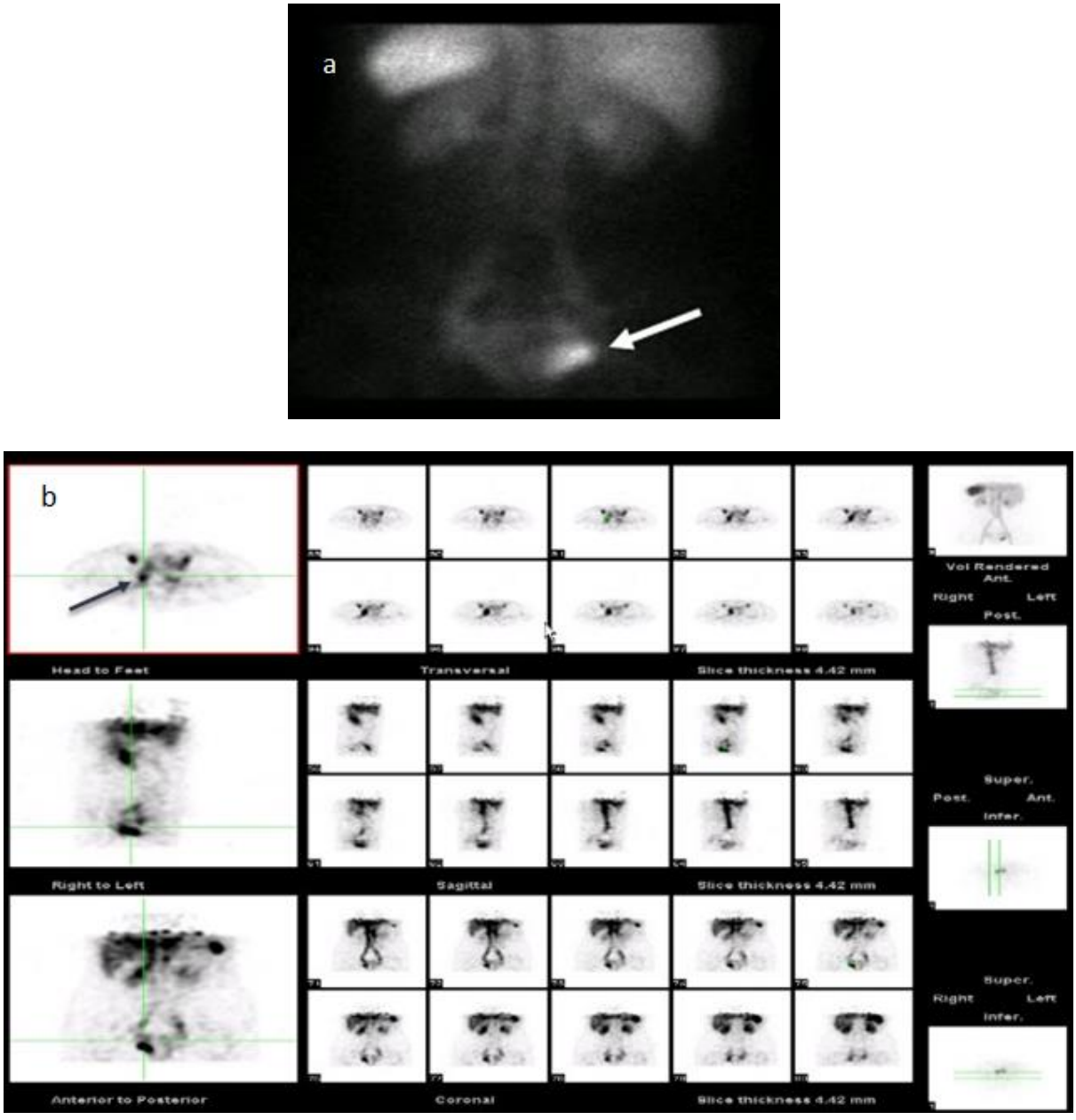

Fig 1. 44 y/o female known case of endometrioma of the right ovary. (a) Posterior view of early images of the [^{99m}Tc]Tc-RBC scan. (b) Corresponding SPECT views showing increased radioactivity accumulation in the region of the right ovary.

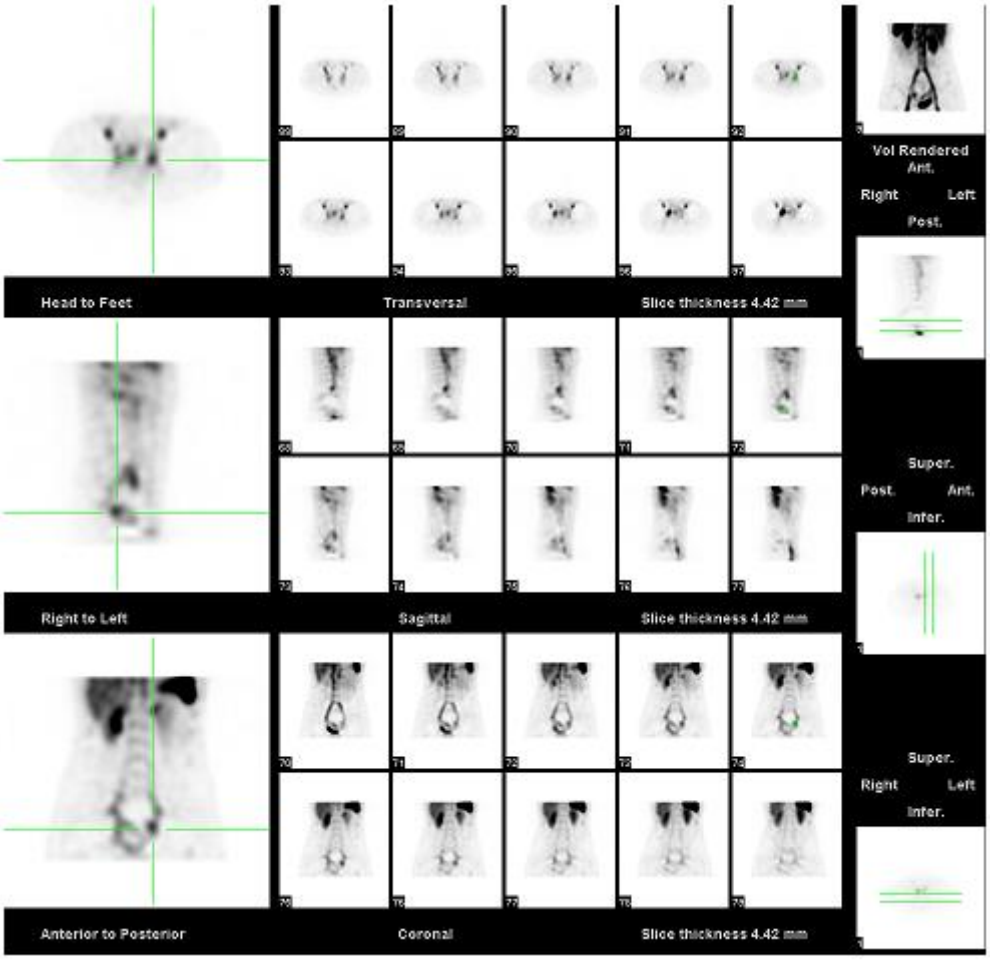

Fig 2. SPECT view of another patient showing increased radiotracer accumulation in the left ovarian region.

Table 4 compares the sensitivity, specificity, PPV and NPV of clinical parameters such as dysmenorrhea, dyschezia, pelvic pain, dyspareunia, dysuria and infertility with biomarkers results such as CA125 and AMH in patients with endometriosis.

DISCUSSION

Endometriosis is the presence of stroma and endometrial gland outside the uterine cavity. It may vary from microscopic endometrium implants to endometriomas (large cysts). The diagnostic procedures for evaluation of endometriosis are often less that satisfactory suffering from shortcomings and limitations. The reason being the pre-operative risk associated with the surgery as well as the presence of dense adhesions in pelvis, which results in the limited access to the Douglas pouch, by laparoscopy. Therefore, there is a need for non-invasive techniques for early possible diagnosis. The need for laparoscopy will likely decrease because of introduction and advancement of non-invasive diagnostic methods [19].

At present, ultrasound is a non-invasive diagnostic method, which has been theoretically successful for diagnosing endometriosis. Ultrasonography is inadequate in showing large implants, pelvic adhesions, peritoneal implants, superficial as well as extra-pelvic lesions [20]. Although both MRI and ultrasound have low sensitivity in diagnosing peritoneal endometriosis, but they are appropriate for diagnosing ovarian endometriomas [21]. In the present study, MRI sensitivity and specificity for the right-sided bleeding sites were 80% and 75% and for the left side 58.3% and 50%, respectively. TVUS demonstrated corresponding 73.3% and 100% on the right and 56.3% and 75% on the left side, respectively. These values for radiolabeled RBC scintigraphy had been 73.3% and 80% on the right and 87.5% and 75% on the left side, respectively (Figures 1 and 2).

Computed tomography is commonly non-specific for diagnosing endometriosis [21, 22].

[^{99m}Tc]Tc-RBC is most commonly used for evaluation of the lower GI bleeding, cardiac mitigated acquisition (MUGA) and liver hemangioma. It is less commonly

used to investigate spleen, measurement of total volume of erythrocyte, diagnosis of gastrointestinal or cerebral vascular malformations and other areas of hemorrhage, post-operative bleeding , deep vein thrombosis, tumor bleeding and low flow bleeding sites that cannot be demonstrated with angiography [23-25]. There are only some case reports showing endometrium with [^{99m}Tc]Tc-RBC, as Cerci et al., [26] study showed in a case with extra-pelvic endometrium implant, which was located at the anterior wall of abdomen in the rectus sheath showing increased radioactive focus.

Other than [^{99m}Tc]Tc-RBC, there has been few scintigraphy studies in endometriosis, with radioactivity labeled anti CA125 Ab, ^{99m}Tc-labeled glutamate peptide-estradiol, [^{131}I]I-TX scintigraphy and few PET case studies. In some studies, MRI detected foci of endometriosis in patients with clinical recurrence, which were congruent with [^{99m}Tc]Tc-RBC findings [25-27].

One study evaluated the endometriotic implants with [^{99m}Tc]Tc-RBC; they assessed whether the active endometriotic implants accumulate radiotracer during menstruation period or not and compared the results with pelvic MRI in patients with recurrent endometriosis. In 27/30 (90%) patients' accumulation of [^{99m}Tc]Tc-RBC were present, which were significant in 26 patients and moderate in 1 patient. In 22 (81.5%) patients, results were concordant with MRI images. The sensitivity of [^{99m}Tc]Tc-RBC was determined as 96%, specificity 29%, negative predictive value 66% and positive predictive value was 81% [13].

Clinical parameters such as pelvic pain, dyspareunia, dysmenorrhea and infertility are insufficient to confirm the diagnosis.

Study limitations

The present study suffers from low sample size additionally the location of the lesions are potentially another limiting factor which might cause false negative results in areas with physiologic accumulation of radioactivity such as uterus and urinary bladder. In these situations, sensitivity may be increased by SPECT-CT, which we did not have at our department, and is the major limitation of this study. In addition, low amount of bleeding might reduce the sensitivity of the test, which can occur in situations such as long-standing consumption of OCP.

For more reliable results, a complementary work with larger sample size and application of hybrid scintigraphic equipment (SPECT/CT) is suggested.

CONCLUSION

The detection of bleeding in the endometrial tissue by [^{99m}Tc]Tc-RBC scintigraphy will depend on minimum volume of radiolabeled extravasated RBCs in the lesion and can potentially be an alternative procedure for the diagnosis of endometriosis.

Acknowledgment

The authors declare no conflict of interest. This study has been approved by the Ethics Committee (IR.SUMS.MED.REC.1396.115) and Institutional Review Board (Study Code No. 13217) of Shiraz University of Medical Sciences and the informed consent form were signed by all of the patients included in the study. The authors would like to thank the staff of nuclear medicine department of Namazi hospital for their cooperation. The authors wish to thank the Research Consultation Center (RCC) at Shiraz University of Medical Sciences for their invaluable assistance in statistical analysis.

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