

The role of ^{99m}Tc -Ubiquicidin (UBI) and ^{99m}Tc -IgG scintigraphies in diagnosis of acute appendicitis: A preliminary result

Hamid Reza Alizadeh Otaghvar¹, Marjan Baniahmad¹, Ali Mahmoud Pashazadeh², Iraj Nabipour³, Hamid Javadi⁴, Leila Rezaei¹, Majid Assadi²

¹Department of Surgery, Faculty of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran

²The Persian Gulf Nuclear Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran

³The Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran

⁴Golestan Research Center of Gastroenterology and Hepatology, Golestan University of Medical Sciences, Gorgan, Iran

(Received 13 July 2013, Revised 14 August 2013, Accepted 25 August 2013)

ABSTRACT

Introduction: Appendicitis is one of the most common surgical emergencies. In spite of the relatively high rate of negative appendectomy, as a result of miss diagnosis, uncertainty of diagnosis still continues to challenge physicians. The objective of this prospective study was to investigate the role of ^{99m}Tc -Ubiquicidin (UBI) scintigraphy in the diagnosis of acute appendicitis and to compare ^{99m}Tc -UBI scintigraphy with ^{99m}Tc -IgG scintigraphy.

Methods: Twelve patients with right lower quadrant pain and suspicious of acute appendicitis were referred to the nuclear medicine imaging center. Radionuclide imaging was performed with ^{99m}Tc -UBI in 8 and ^{99m}Tc -IgG in 4 patients. Ultrasonography, Alvarado scoring and histopathological examinations were also performed as additional diagnostic tests.

Results: Reports from ^{99m}Tc -IgG and ^{99m}Tc -UBI scintigraphies of all patients were negative.

Conclusion: This study may conclude that ^{99m}Tc -IgG scintigraphy and ^{99m}Tc -UBI scintigraphy in the detection of appendicitis do not have adequate efficacy. However, in order to better evaluate ^{99m}Tc -IgG and ^{99m}Tc -UBI scintigraphy, a comprehensive study on a large number of patients with clinical suspicious of acute appendicitis would be more helpful.

Key words: ^{99m}Tc -IgG scintigraphy; ^{99m}Tc -UBI scintigraphy; Acute appendicitis; Ultrasonography; Alvarado scoring

Iran J Nucl Med 2014;22(1):7-10

Published: December, 2013

<http://irjnm.tums.ac.ir>

Corresponding author: Ali Mahmoud Pashazadeh, The Persian Gulf Nuclear Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran. E-mail: a.pashazadeh@bpums.ac.ir

INTRODUCTION

The accuracy of a clinical diagnosis is the first challenging step for every clinical practice. Good treatment is usually the result of a good diagnosis with high accuracy. In some emergency situations, which need treatment or surgery, rapid detection plays a vital role in the treatment outcome. A common surgical emergency, in which accurate diagnosis is still a challenging task, is acute appendicitis. Results of studies on the subject reveals that the rate of negative appendectomy is relatively high and about 20–40% of patients with appendicitis are misdiagnosed [1].

Although, negative appendectomy is considered relatively harmless but surgery by itself is an economic burden and may cause complications such as post appendectomy infections [2]. Various detection techniques have been developed to reduce negative appendectomy rates as much as possible. Among the procedures and techniques used for diagnosis of appendicitis, operation and histopathological examinations are considered gold standards [3]. In spite of absolute diagnostic values of these examinations they are invasive with potential complications and practical limitations. Application of imaging techniques in the diagnosis of appendicitis as non-invasive diagnostic procedures can be used prior to invasive methods in order to determine if an operation is necessary. In regard to imaging modalities, radionuclide imaging or nuclear medicine procedures have the advantage of early detection, which allows the early diagnosis of appendicitis in early phase when infectious process is just in the beginning [4]. In this stage, clinical symptoms are minimal and the patient may appear healthy therefore diagnostic potential of nuclear medicine can be used as a promising technique in the early detection of appendicitis.

Various radiopharmaceuticals can be used for this purpose. Recently ^{99m}Tc labeled with UBI has been proposed as an imaging radiopharmaceutical in diagnostic nuclear medicine. UBI is a cationic human antimicrobial peptide fragment with molar weight of 1.69 kDa and 6 positively charged residues and results of the studies indicate that ^{99m}Tc -UBI binds to bacteria and is accumulated at sites of infection [5]. Another agent which its ability in detecting a variety of infections, including those of the chest, abdomen, hip and bone has been reported extensively in the literature is technetium- ^{99m}Tc -labelled polyclonal human immunoglobulin G (^{99m}Tc -IgG) [3].

Therefore, the aim of the present study was to evaluate diagnostic value of ^{99m}Tc -UBI and ^{99m}Tc -IgG scintigraphy in the detection of acute appendicitis.

METHODS

This prospective study was conducted in the Persian Gulf Nuclear Medicine Research Center and Fatemeh-Zahra Hospital in the period of March 2010 to March 2011. All suspected patients with acute right lower quadrant abdominal pain were admitted. The Alvarado scores were computed, and then patients with a score of 5 or 6 also patients suffering from acute right lower quadrant abdominal pain for more than three days were evaluated by ultrasonography then were referred to the nuclear medicine department. A total of 12 patients were referred to undergo nuclear medicine scintigraphy.

This study complies with the declaration of Helsinki and was approved by the Institutional Ethics Committee of the University of Medical Science. All patients provided written informed consent.

Imaging protocols

For ^{99m}Tc -IgG scintigraphy, a human nonspecific polyclonal immunoglobulin for intravenous administration was used. Following the preparation of solution of IgG (pH of 7.4, concentration of 10 mg/mL in 0.01 M phosphate-buffered saline), 740 MBq (20 mCi) of ^{99m}Tc which was previously provided by the Iran Atomic Energy Agency was added to it then the resulted solution was incubated for 20 min at room temperature.

Each vial of UBI contained 40 μg peptide dissolved in 10 μL 0.01 mol/L acetic acid, 5.0 μL of stannous ions from the standard pyrophosphate kit and 8.0 μL borohydrate prepared as standard solution of 0.7 mg/mL sodium borohydrate in 0.1N NaOH. Vials of UBI were maintained at -5°C in the refrigerator and PH of the solution was maintained at 6 to 7. In order to provide ^{99m}Tc -UBI, 740 MBq (20 mCi) of ^{99m}Tc was added to the vial of UBI, the content was incubated for 10 to 15 min then 0.9% saline was added to the vial to bring the constituted volume to 2.0 mL.

Immediately after injection of ^{99m}Tc -UBI or ^{99m}Tc -IgG, dynamic acquisition for 60 s for each frame was done for 90 min followed by static images every 15 min for 2-4 hours.

Static scintigraphy of ^{99m}Tc -IgG and ^{99m}Tc -UBI was performed by a high resolution double headed SPECT scintillation camera (ADAC Genesys Malpitas, CA, USA) with a low-energy all purpose collimator using a matrix of 128×128 on a 20% window at a 140-keV peak. Scintigraphy scans were analyzed visually by two nuclear medicine physicians, who were not aware of the clinical symptoms or work up of the patients.

Table 1. Statistical parameters of ^{99m}Tc-UBI Scintigraphy, ^{99m}Tc-IgG Scintigraphy, ultrasonography (US) and Alvarado scoring in detection of acute appendicitis.

	Group 1(8 patients)			Group 2(4 patients)		
	^{99m} Tc-UBI	US	Alvarado (score≥7)	^{99m} Tc-IgG	US	Alvarado (score≥7)
Sensitivity	0%	50%	100%	0%	50%	100%
Specificity	0%	100%	100%	0%	0%	100%
PPV	0%	100%	100%	0%	100%	100%

RESULTS

^{99m}Tc-UBI scan

The Alvarado score was computed for 8 patients (6 men and 2 women) with a mean age of 20.75 y (16-25 y) suspected to have acute appendicitis. Four patients received a score of 9 and 4 other patients' score of 5-7. Ultrasonography scanning was performed on 6 out of 8 patients; in 2 cases appendicitis was suggested. The pathology report, after the surgery, proved appendicitis for all patients in good agreement with surgeon exams before and during the surgery. Microbiologic sampling of appendix revealed *E. coli* and *pseudomonas* in 3 patients. The results of ^{99m}Tc-UBI scanning in all patients were negative (Table 1).

^{99m}Tc-IgG scan

Four patients (3 men and 1 woman) with a mean age of 34 y (19-63 y) were evaluated to detect acute appendicitis. Pathology reports and observations during surgery proved appendicitis for all patients with Alvarado score of 9. Ultrasonography scanning was performed on 3 patients (2 men and 1 woman) but appendicitis was detected only for the woman. Appendicitis sample culturing of 2 patients had negative results. Reports from ^{99m}Tc-IgG scanning of the patients were negative for all patients.

DISCUSSION

The present study is the first attempt to evaluate the diagnostic value of ^{99m}Tc-UBI scintigraphy in acute appendicitis. There have been extensive studies for ^{99m}Tc-UBI scintigraphy for a variety of infections including bone infections, soft tissue infections, prostheses and fever of unknown origin (FUO) but there is no report regarding ^{99m}Tc-UBI scintigraphy for appendicitis. Akhtar et al., investigating antimicrobial peptide ^{99m}Tc-Ubiquicidin potential as human infection imaging agent, reported the overall sensitivity, specificity, and accuracy as 100%, 80% and 94.4%, respectively [6]. We studied the accuracy

of ^{99m}Tc-UBI scan in detection of osteomyelitis in comparison to ^{99m}Tc-methylene diphosphonate scintigraphy and magnetic resonance imaging. Results of our previous study showed detection accuracy of 100% for ^{99m}Tc-UBI scintigraphy of osteomyelitis. We found that for fast detection of osteomyelitis, ^{99m}Tc-UBI is a promising modality with high accuracy [7].

Sepúlveda-Méndez et al., studying ^{99m}Tc-UBI for detecting infection foci in patients with fever, reported that specificity, sensitivity, accuracy, PPV and NPV of ^{99m}Tc-UBI for localizing infection foci was 95.35%, 97.52%, 96.62%, 96.72% and 96.47% respectively. They concluded that ^{99m}Tc-UBI could be the gold standard in molecular imaging of infection sites [8]. Relative high accuracy, sensitivity and specificity of ^{99m}Tc-UBI scintigraphy in the detection of infections indicate high potential of this radionuclide as an infection seeking agent. Such promising results are partly due to the agent inducing infection. *Staphylococcus aureus* is one of such infectious agents. Akhtar et al. evaluated the bacterial infection seeking potential of ^{99m}Tc-UBI in *Staphylococcus aureus* and *E. coli* induced infections. They found that ^{99m}Tc-UBI accumulates less in *E. coli* infections than in *Staphylococcus aureus* infections [9]. Because *E. coli* is the most common infection agent involved in appendicitis, it is expected that the diagnostic value of ^{99m}Tc-UBI scintigraphy for appendicitis is not as efficient as for other types of infections in which *Staphylococcus aureus* is the predominant infectious agent.

Furthermore, ^{99m}Tc-IgG scintigraphy has been used in the detection of acute appendicitis by Wong et al. on 35 patients suspected to have acute appendicitis. Results of that study showed sensitivity, specificity, accuracy, PPV and PNV of 91%, 100%, 94%, 100% and 86%, respectively. They concluded that ^{99m}Tc-IgG scintigraphy of acute appendicitis can be a simple, rapid, and definitive technique [10]. Wong et al., in another attempt, evaluated efficacy of ^{99m}Tc-IgG for the early localization and detection of acute appendicitis in an animal model and suggested that ^{99m}Tc-IgG may have potential in the early detection of acute appendicitis when a rapid diagnosis is

needed [11]. Asadi et al., investigated ^{99m}Tc -polyclonal IgG scanning in the detection of acute appendicitis. The images obtained by planar and SPECT scan were subjected to visual and quantitative analysis. The sensitivity and specificity of planar and SPECT images for diagnosis of appendicitis were 19-24% and 100% and, 62% and 68%, respectively. They concluded that because of the low sensitivity and moderate NPV (62%) of ^{99m}Tc -IgG scanning, it is not a suitable tracer for diagnosis of appendicitis [12].

Findings from this study showed poor sensitivity, specificity, PPV and NPV for ^{99m}Tc -IgG scintigraphy of appendicitis, however previous studies have shown more acceptable diagnostic results. In comparison with the above-mentioned studies, they used both qualitative and semi-quantitative analyses in a larger number of patients but in the current study, only qualitative analysis was used because we thought that a suitable radiotracer for detection of acute appendicitis should be obviously positive at first in the visual assessment. Also due to lack of capabilities of these scans in the diagnosis of acute appendicitis in planar views, we discontinued the requirement of new patients into the study. However, one main reason for this difference may have been in the number of patients attended to our study.

Our study suffers from one main limitation regarding number of patients attended in this research. Therefore in order to provide a more detailed comparison of the diagnostic value of ^{99m}Tc -IgG and ^{99m}Tc -UBI in acute appendicitis, similar study with larger sample is recommended.

CONCLUSION

This study may conclude that ^{99m}Tc -IgG scintigraphy and ^{99m}Tc -UBI scintigraphy in the detection of appendicitis do not have sensible efficacy. However, in order to better evaluate ^{99m}Tc -IgG and ^{99m}Tc -UBI scintigraphy, much larger study on patients suspected to have acute appendicitis would be necessary.

Acknowledgments

This study was performed as a thesis of Marjan Baniahmad with the sponsorship of Bushehr University of Medical Sciences (grant no. 876). We thank to colleagues at our institutes especially SR. Mosavi and M. Kassaian for their technical help and assistance with data acquisition.

REFERENCES

1. Kalan M, Talbot D, Cunliffe WJ, Rich AJ. Evaluation of the modified Alvarado score in the diagnosis of acute appendicitis: a prospective study. *Ann R Coll Surg Engl*. 1994 Nov;76(6):418-9.

2. Partrick DA, Janik JE, Janik JS, Bensard DD, Karrer FM. Increased CT scan utilization does not improve the diagnostic accuracy of appendicitis in children. *J Pediatr Surg*. 2003 May;38(5):659-62.
3. Dey S, Mohanta PK, Baruah AK, Kharga B, Bhutia KL, Singh VK. Alvarado scoring in acute appendicitis-a clinicopathological correlation. *Indian J Surg*. 2010 Aug;72(4):290-3.
4. Rypins EB, Evans DG, Hinrichs W, Kipper SL. Tc-99m-HMPAO white blood cell scan for diagnosis of acute appendicitis in patients with equivocal clinical presentation. *Ann Surg*. 1997 Jul;226(1):58-65.
5. Gandomkar M, Najafi R, Shafiei M, Mazidi M, Goudarzi M, Mirfallah SH, Ebrahimi F, Heydarpor HR, Abdie N. Clinical evaluation of antimicrobial peptide [(99m)Tc/Tricine/HYNIC(0)]ubiquicidin 29-41 as a human-specific infection imaging agent. *Nucl Med Biol*. 2009 Feb;36(2):199-205.
6. Akhtar MS, Qaisar A, Irfanullah J, Iqbal J, Khan B, Jehangir M, Nadeem MA, Khan MA, Afzal MS, Ul-Haq I, Imran MB. Antimicrobial peptide 99mTc-ubiquicidin 29-41 as human infection-imaging agent: clinical trial. *J Nucl Med*. 2005 Apr;46(4):567-73.
7. Assadi M, Vahdat K, Nabipour I, Sehhat MR, Hadavand F, Javadi H, Tavakoli A, Saberifard J, Kalantarhormozi MR, Zakani A, Eftekhari M. Diagnostic value of 99mTc-ubiquicidin scintigraphy for osteomyelitis and comparisons with 99mTc-methylene diphosphonate scintigraphy and magnetic resonance imaging. *Nucl Med Commun*. 2011 Aug;32(8):716-23.
8. Sepúlveda-Méndez J, de Murphy CA, Rojas-Bautista JC, Pedraza-López M. Specificity of 99mTc-UBI for detecting infection foci in patients with fever in study. *Nucl Med Commun*. 2010 Oct;31(10):889-95.
9. Akhtar MS, Iqbal J, Khan MA, Irfanullah J, Jehangir M, Khan B, Ul-Haq I, Muhammad G, Nadeem MA, Afzal MS, Imran MB. 99mTc-labeled antimicrobial peptide ubiquicidin (29-41) accumulates less in *Escherichia coli* infection than in *Staphylococcus aureus* infection. *J Nucl Med*. 2004 May;45(5):849-56.
10. Wong DW, Vasinraee P, Spieth ME, Cook RE, Ansari AN, Jones M Jr, Mandal A. Rapid detection of acute appendicitis with Tc-99m-labeled intact polyvalent human immune globulin. *J Am Coll Surg*. 1997 Dec;185(6):534-43.
11. Wong DW, Mandal A. Technetium-99m IgG immunodetection of acute appendicitis in rats. *Nucl Med Biol*. 1996 May;23(4):473-8.
12. Asadi M, Mehrabi Bahar M, Sadeghi R, Jangjo A, Dabbagh Kakhki V, Zakavi SR. Value of polyclonal human immunoglobulin tagged with ^{99m}Tc for detecting acute appendicitis in patients with intermediate probability of appendicitis. *World J Surg*. 2011 Aug;35(8):1798-802.