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ORIGINAL ARTICLES

COMPARISON OF COMBINED ORAL AND IV CONTRAST-ENHANCED VERSUS SINGLE IV CONTRAST-ENHANCED MDCT FOR THE DETECTION OF ACUTE APPENDICITIS

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Objective: **The aim of our study was to compare the diagnostic ability of oral added intravenous (IV) contrast-enhanced multidetector computed tomography (MDCT) versus only IV contrast-enhanced MDCT in diagnosing of acute appendicitis.**

Materials and methods: **MDCT images of 200 patients were evaluated prospectively in this study. Patients were randomized into one of two groups: Group 1 (Gp1) patients underwent 16-MDCT performed with oral and IV contrast-enhanced and Group 2 (Gp2) subjects underwent 16-MDCT with only IV contrast-enhanced protocol. Final decision was based on histopathologic operative data and follow-up of patients.**

Results: **In Gp1, Reader1 had 96.9% and 98.5% and Reader2 had 84% and 94.7% sensitivity and specificity values respectively. For Gp2, the values for Reader1 were 81% and 94%. For Reader2 in Gp2, the values were 76% and 91%. We achieved higher sensitivity and specificity values with combined contrast administration versus only IV contrast-enhanced MDCT imaging. However, there was no statistically significant differences between two readers in the AUC values of each group for the detection of acute appendicitis.**

Conclusion: **It is statistically concluded that oral contrast do not contribute to the a better accuracy. So in the routine practice, oral contrast has not to be recommended.**

Key-word: Appendicitis.

Acute appendicitis is the most common cause of acute abdominal pain that requires abdominal surgery (1, 2). Appendicitis may present a wide variety of clinical manifestations, and the diagnosis is difficult even by the most experienced clinicians (3). Early diagnosis and intervention to avoid perforation is very important, as is the standard of care. The diagnosis of appendicitis is established through a combination of clinical, laboratory, and radiological features, especially computed tomography (CT) imaging. CT is increasingly used in the evaluation of patients with suspected acute appendicitis with excellent sensitivity and accuracy. By the beginning to use multi-detector row CT (MDCT) systems technology affords a considerable reduction in scanning time and an improvement in image quality with minimal degradation from motion artefacts. Sensitivity and specificity values of abdomen MDCT imaging in acute appendicitis were reported to be 80-100% and 91-99% respectively (4-7). However, controversy still persists about which is the most effective contrast application technique for the evaluation of appendicitis in CT imaging. A variety of CT approaches have been advocated including unenhanced, IV contrast-enhanced, oral contrast enhanced, rectal contrast enhanced and combination of contrast applications in the diagnosis of appendicitis (7-9). The time to perform a scan varies significantly between these different methods of MDCT imaging. Oral and IV contrast combination may be helpful in some difficult cases for the prompt diagnosis of acute appendicitis.

The purpose of our prospective study was to conduct a randomized trial to compare the diagnostic performance of IV and oral contrast-enhanced MDCT versus only IV contrast-enhanced MDCT in patients presenting with acute nontraumatic abdominal pain clinically suspected to be secondary to acute appendicitis.

Materials and methods

The participants were 200 adult patients who presented with clinical signs and symptoms that suggested acute appendicitis. All were enrolled between March 2008 and October 2010. On admission, all patients had right lower or mid quadrant pain, 25% had nausea, 10% had vomiting and low-grade fever. Patients were 18 years old and older with nontraumatic abdominal pain. Thus, we excluded patients with possible contrast allergy, pregnant ones and traumatic cause of abdominal pain. The physicians of emergency department (ED) in screening for and recruiting suggested patients with acute nontraumatic abdominal pain for this study.

Two hundred patients (113 men, 87 women; mean age of men, 32 years; mean age of women, 38 years) were included in this research. The patients whom suspected acute appendicitis or other acute pathologies (diverticulitis, small-bowel obstruction, etc.) were sent to radiology department for MDCT scan after had evaluated in ED. All patients were randomized into one of two groups: Group 1 (Gp1) was composed of patients with combined oral and IV contrast-enhanced abdominal MDCT, and Group 2 (Gp2) was consisted of only IV contrast-enhanced MDCT patients. Gp1 included 58 men and 42 women with a mean age of 38 years (range, 18-74 years), and Gp2 consisted of 62 men and 38 women with a mean age of 42 years (range, 20-66 years).

This study was approved by the institutional review board of our

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Table I. — Comparison of the CT diagnosis and exact results of two groups for two readers.

Reader 1	CT scanned total cases	True (+)	True(-)	False (+)	False(-)	Total
Gp1 (IV + Oral contrast contrast)	100	31	67	1	1	100
Gp2 (IV contrast)	100	21	71	4	4	100
Total	200	52	138	5	5	200
Reader 2	CT scanned total cases	True (+)	True(-)	False (+)	False(-)	Total
Gp1 (IV + Oral contrast contrast)	100	30	66	2	2	100
Gp2 (IV contrast)	100	18	67	7	8	100
Total	200	48	133	9	10	200

Faculty. Informed consent was obtained from all patients.

CT scanning

All CT scans had been obtained using 16-section MDCT (Sensation 16, Siemens Medical Solutions, Erlangen, Germany, 2003). All patients within two groups have been scanned in precontrast phase firstly. This procedure is the routine protocol of our radiology department for all abdomen CT patients. In Gp1 for oral positive contrast protocol, patients had been given 1500 mL of water solution with 3% Meglumin (Telebrix 35, Guerbet, France) approximately 60 minutes before MDCT scanning. After precontrast scanning all patients were scanned with IV contrast-media administration. In this protocol, after IV administration of 100 mL of Ioversol (350 mgI/mL, Optiray, Covidien, Tyco, USA) at a rate of 3 mL/sec and after 60 sec delayed portal phase, a CT scan of the entire abdomen from the dome of the diaphragm through the pubic symphysis was performed. The MDCT parameters selected were 5-mm thick slices, 0.75 pitch, 120 kV, and 100 mA. Images of all patients were recorded to CD for archiving as a seperate series for all MDCT studies.

Image analysis

All CT images were evaluated by two radiologists with over 5 years experience in interpreting MDCT imaging of the abdomen in their daily clinical practice. They were not informed of the results of the imaging findings or of the final diagnosis. The analyses of the images of the 2 groups were based on reviews of soft copies which were available on workstation (Leonardo, Siemens Medical Solutions, Germany, 2002). The radiologists interpreted the studies using multiplanar reconstruction sections. Each reviewer was given a sequential list of all patients by an independent researcher. Interpretations of the two groups (Gp1 and Gp2) had been done seperately at the same interval to prevent recall bias. Radiologists evaluated the scans for the presence of acute appendicitis with a five-point Licert scala according to following scores; 1: definitely abscent, 2: probably abscent, 3: indeterminate, 4: probably present, and 5: definitely present. The primary diagnostic criterias for the diagnosis of acute appendicitis were visualization of a thickened appendix (width > 6 mm), mural thickening, and mural enhancement with or without periappendiceal stranding. With oral contrast-added images, hyperenhancement of the appendix as well as absence of filling appendix lumen with oral contrast was considered another positive criteria.

For patients whom did not undergo an operation, medical follow-up data of patients was undertaken by another researcher of study who was blinded to MDCT results to determine clinical outcomes. This process also was made by follow-up information obtained from patient, 1 day and 1 week after discharge from the hospital using telephone questionnaires and medical record reviews. Standard of reference of this study was determined by this process. On the other side, once the interpretations were compared with the standard of reference, radiologists retrospectively detected false-negative and false-positive interpretations by consensus to provide an optimal explanation for each misinterpretations.

Precise diagnosis of acute appendicitis was considered only when patients underwent surgical operation and histopathologic analysis yielded "acute appendicitis".

Statistical analysis

Once all interpretations were completed by the two radiologists, by an independent researcher reviewed the data set for determine interobserver agreement. In order to assess interobserver agreement for the evaluation of the two groups, we calculated the Cohen's kappa statistic for two observers. Agreement between the blinded radiologists was reported in terms of kappa values, those values up to 0.40 indicated poor agreement, values of 0.41-0.60 indicated moderate agreement, those between 0.61-0.80 indicated good agreement, and values greater than 0.81 indicated excellent agreement. Interpretations scored 1 and 2 were considered negative diagnosis, and score 4 and 5 were considered positive diagnosis. Interpretations scored "indeterminate"-3 were evaluated false-positive or false-negative depending on whether the standard of reference revealed the diagnosis to be absent or present, respectively. Diagnosis of two radiologists were collected and compared with the standard of reference by independent researcher of this study to calculate the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) respectively. Using the Fisher's exact test, we compared the sensitivity and specificity values of the combined interpretations of two groups for the diagnosis of acute appendicitis.

Receiver operating characteristic (ROC) curves were created for comparing of two groups with the results of two radiologists. Areas under the ROC curves (AUCs) were calculated with SPSS analysis program (SPSS for Windows 1, SPSS Inc. Chicago, Ilionis, USA, 2006). AUCs, or A_z, that

Table II. — Results: AUC values.

Reader	Group 1			Group 2			
	AUC	95% CI		AUC	95% CI		
		Lower	Upper		Lower	Upper	p
1	0,972	0,921	1,000	0,993	0,982	1,000	0,431
2	0,962	0,909	1,000	0,989	0,971	1,000	0,343
p	0,790			0,712			

AUC: Area under curve CI: Confidence interval.

Table III. — Results: diagnosis of acute appendicitis.

Reader		Sensitivity	Specificity	PPV	NPV
1	Gp1	96.9% (82,0-99,8)	98,5% (91,0-99,9)	96.9% (82,0-99,8)	98,5% (91,0-99,9)
	Gp2	81% (59-94)	94% (86-98)	84,0% (63,1-94,7)	94,7% (86,2-98,3)
2	Gp1	84% (63,1-94,7)	94,7% (86,2-98,3)	93,7% (77,8-98,9)	97,1% (88,8-99,5)
	Gp2	76 % (57-88)	91% (82-96)	72,0% (50,4-87,1)	89,3% (79,5-94,9)

*PPV: Positive predictive value, ** NPV: Negative predictive value, Gp1 patients evaluated with combined (oral and IV) contrast and Gp2 subjects performed with only IV contrast-enhanced. Confidence Interval(CI).

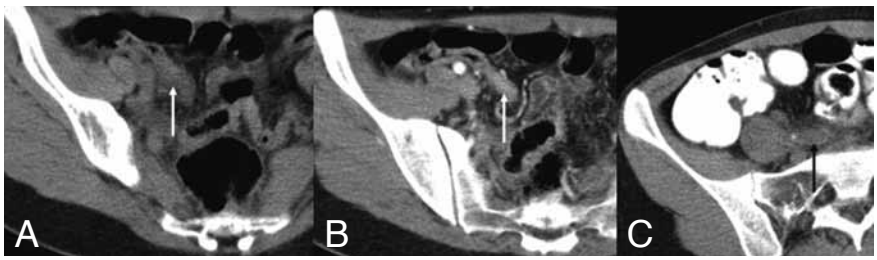

Fig. 1. — Evaluation of acute appendicitis in pre-contrast image (A), IV contrast-enhanced image (B) and combined oral and IV contrast-enhanced image (C). Appendicolith is also seen in oral and IV contrast added image (C).

Fig. 2. — Marked enlargement appendix with mild periappendiceal fat stranding, this case was the one of false-positive interpretation. Axial oral contrast-enhanced (A), oral and IV contrast added (B), and coronal reformatted image of oral + IV contrast-enhanced images (C).

account for variability among modalities (Gp1 and Gp2), among reviewers (two reviewers), and among cases. Differences between the detection ratios of the two groups were compared by "z test for two proportion", where a *P* value of less than 0.05 was considered a statistically significant difference.

Results

Twenty-five of the 100 patients in Gp1 and 18 of the 100 patients in Gp2 had a exact diagnosis of acute appendicitis with MDCT and confirmed by histopathologically (Fig. 1-4) . In the evaluation of reader 1, there were 31 true-positive, 67 true-negative, one false-positive, and one false-negative interpretations for Gp1. However, there were 21 true-positive, 71 true-negative, and four false-positive and negative interpretations detected for Gp2. For reader 2, there were 30 true-positive, 66 true-negative, two false-positive, and false-negative interpretations for Gp1. Thus, there were 18 true-positive, 67 true-negative, and 7 false-positive and eight false-negative interpretations detected for Gp2 (Table I). However, on retrospective consensus evaluation of the false-positive misdiagnosis in Gp2 and Gp1, the radiologists thought that the all patients were extremely thin patients and lack of periappendiceal fat could be play a great role in misdiagnosis.

In performing ROC curves for two radiologists, AUCs were calculated. For the two readers, the AUCs for the ROC for Gp1 were 0.97 and 0.96. For Gp2, they were both 0.99. *P* values were calculated by "z test for two proportion". There was no statistically significant differences between two readers in the AUC values in each group, *p* values were 0.79 and 0.71 for Gp1 and Gp2 respectively. Also, no statistically significant differences between Gp1 and Gp2 in the AUC values for each reader were found and *p* values were 0.43 and 0.34 for reader 1 and 2 respectively (Table II).

Using Fisher's exact test, comparison of sensitivity and specificity

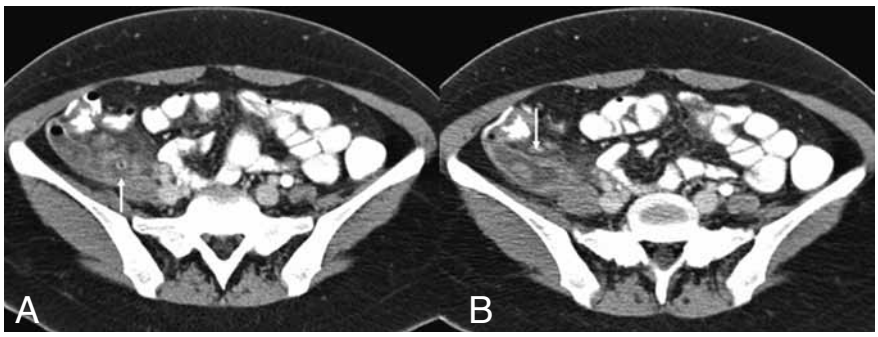

Fig. 3. — Early acute appendicitis with calcified appendicolith in lumen of inflamed appendix (arrow) with oral and IV contrast-enhanced image (A-B).

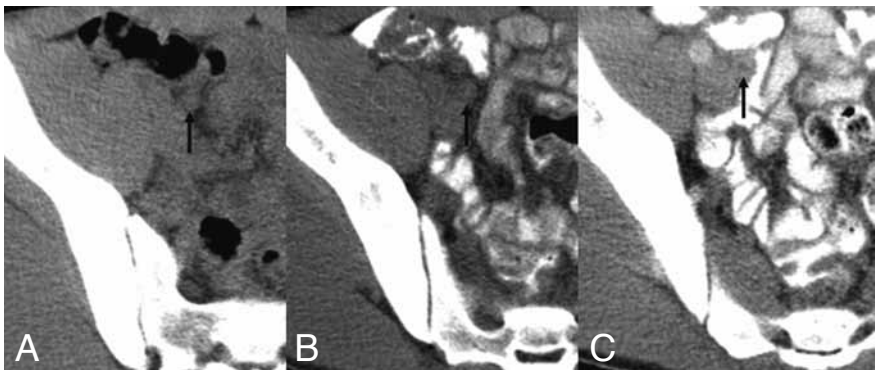

Fig. 4. — Acute appendicitis in a 17-year-old boy with little retroperitoneal fat. Unenhanced CT scan shows undefined visualization of inflamed appendix (A). With application of only oral contrast, the appendix is more defined (B). Finally, with oral and IV contrast administration inflamed appendix (arrow) is seen clearly on axial scan (C).

between the combined interpretations for the diagnosis of acute appendicitis were calculated. Although there was no significant difference in sensitivity or specificity for the diagnosis of acute appendicitis. For Group 1 (Gp1), Reader 1 had 96.9% (95%CI, 82%-99.8%) and 98.5% (95%CI, 91%-99.8%) and Reader 2 had 84% (95%CI, 63.1%-94.7%) and 94.7% (95CI, 86.2%-98.3%) sensitivity and specificity values respectively. For Group 2 (Gp2), the performance values for Reader 1 were 81% (95%CI, 59%-94%) and 94% (95%CI, 86%-98%). For Reader 2 in Gp 2, the values were 76% (95%CI, 57%-88%) and 91% (95%CI, 82%-96%) respectively for the diagnosis of acute appendicitis (Table III) .

For evaluation of inter-observer agreement between two radiologists, the kappa value for Gp 1 (0.931) was smilar to that of Gp2 (0.899) kappa value. These values were indicated excellent inter-observer agreement between two radiologists.

Discussion

Primary diagnostic criteria for acute appendicitis have been defined as visualization of an enlarged appendix greater than 6 mm in diameter. Secondary criterias were wall thickening and enhancement, appendicolith, periappendiceal fat stranding, free fluid in right lower quadrant or pelvis, periappendiceal abscess, small bowel obstruction, and mural thickening of cecum (1). The value of computed tomography (CT) and MDCT imaging in the diagnosis of appendicitis has been the subject of multiple research projects (10-12). Unless completely replaced by phlegmon or abscess, CT should allow for indetification of an enlarged appendix, appearing in a tubular or circular form with axial orientation or coronal reformatting of MDCT images. Various CT protocols have been described recent years but, -no definitive CT contrast application- technique has been established for the evaluation of acute appendicitis. Furthermore, different CT or MDCT contrast protocols are used in the same diagnostic department in routine imaging. The major subjects of discussion are the uses and modes of administration of contrast materials (8-10).

Most contrast-enhanced CT techniques for diagnosis of acute appendicitis that have been described previously have used materials of oral contrast, rectal contrast, both oral and rectal contrast or a combination of IV and other contrast materials (8-10, 13-16). However, the use of unenhanced CT (without oral and IV contrast media) in patients with suspected appendicitis has also been reported. Malone et al used an unenhanced CT technique and they reported a sensitivity of 87%, a specificity of 97% and an accuracy of 93% for the diagnosis of appendicitis (17).

In the evaluation of acute nontraumatic abdominal pain, studies have shown increased sensitivity in the diagnosis of acute appendicitis with the application of IV contrast media. Several investigators (1, 14, 18) have shown that IV contrast-enhanced CT is an accurate imaging technique for detecting acute appendicitis. In one of the most-cited references about contrast applications, Rao et al. demonstrated that focused CT of the lower abdomen,- after administration of combined oral and colonic contrast material or colonic contrast material alone, had better diagnostic performance (7, 8).

The benefits of oral contrast for diagnosis of acute appendicitis have been questioned and investigators have shown that oral contrast media does not reliably fill the appendicieal lumen of normal patients and, therefore a lack of filling of lumen is not always indicator of acute appendicitis. However, filling of the appendicieal lumen may help to exclude acute appendicitis, this sign is seen almost 61% of normal appendicitis (9).

A number of researchers using contrast-enhanced CT with both IV and oral contrast materials reported that sensitivity, specificity and accuracy ranges in their diagnoses of acute appendicitis were 92-98%, 85-100%, and 90-99% respectively (13, 14, 18, 19). Anderson et al. demonstrated that, there is no significant difference for diagnosing appendicitis between oral and IV enhanced MDCT with only IV enhanced MDCT by using 64-slice MDCT (20). This conclusion was the same direction of our results.

However until today, these studies have not shown us a current standardized CT protocol for the diagnosis of acute appendicitis. At our institution, we are using two contrast- media protocols with MDCT for evaluating abdominal imaging. One of these protocol is only IV contrast applied MDCT , and the other one is oral and IV combined enhanced MDCT. Choosing the proper protocol is a decision made by the radiologist of abdominal CT team due to the patient's urgency, clinical and laboratory findings. Generally oral added protocol will be selected for suspected acute appendicitis cases if the patient could be wait nearly one hour. This period is necessary for optimal enhancing of intestines.

General surgery team and anesthesists were generally accepted almost one hour delay for oral contrast imaging especially in suspected appendicitis cases with subacut progress. By the way, highly suspected acute apandicitis with heavy clinical symptoms did not refered to radiology department from emergency room for oral contrast added abdomen CT imaging.

We achieved higher sensitivity and specificity values with combined contrast administration than we did with only IV contrast-enhanced MDCT imaging. Due to the filling of the appendix with oral contrast, in Gp 1 false negative cases were significantly lower than in Gp2 cases (1 and 2 interpretations for Gp1 versus 4 and 8 interpretations for Gp2 for reader 1 and 2 respectively). On the other side, Fisher's exact test demonstrated that, in comparison with sensitivity and specificity of two groups, there was no significant difference for the diagnosis of acute appendicitis. Evaluation of under the ROC curves showed that, there was no statistically significant differences in the AUC values found between the Gp1 and Gp2.

We acknowledge several limitations to our study. We were unable to provide exact denominator of all patients evaluated for acute nontraumatic abdominal pain. On the other side, radiologists in this research whom evaluated the MDCT images, scrutinized the MDCT images for possible acute appendicitis. Due to this process, increasing of sensitivity and specificity may be done in practice. Another limitation was the only convenience patients enrolled this study, and this given rise to an selected population for this study.

In conclusion, it is statistically concluded that oral contrast do not contribute to the a better accuracy. So in the routine practice, oral contrast has not to be recommended. However, in selected patients with thin bodies, oral contrast-added MDCT imaging may be helpful for the diagnosis of acute apendicitis by increasing the sensitivity and specificity level little higher.

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