

## Original Contribution

Spot urinary 5-hydroxyindoleacetic acid is not an ideal diagnostic test for acute appendicitis<sup>☆,☆☆</sup>Ahsan Rao<sup>a,\*</sup>, Michael Wilson, MSc<sup>a</sup>, Gwen Kennedy<sup>b</sup>, Devender Mittapalli<sup>a</sup>, Iain Tait, PhD<sup>a</sup>, Afshin Alijani, PhD<sup>a</sup><sup>a</sup> Department of Surgery, Ninewells Hospital and Medical School, Dundee DD2 9SY, UK<sup>b</sup> Immunoassay Biomarker Core Laboratory, School of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

## ARTICLE INFO

## Article history:

Received 6 May 2016

Received in revised form 22 May 2016

Accepted 24 May 2016

## ABSTRACT

**Background and purpose of the study:** There is growing evidence to suggest the use of urinary 5-hydroxyindoleacetic acid (5-HIAA) test to help with the diagnosis of appendicitis. The aim of our study was to establish whether urinary 5-HIAA could be used as an effective diagnostic test for acute appendicitis.

**Design and methods:** A prospective double-blinded study was carried out from December 2014 to October 2015. Patients admitted to the emergency surgical ward of a teaching hospital with suspected appendicitis were included in the study. The diagnostic accuracy of the test was measured by receiver operating characteristic curve.

**Results:** Ninety-seven patients were divided into 2 groups: acute appendicitis (n = 38) and other diagnosis (n = 59). The median value of urinary 5-HIAA was 24.19 μmol/L (range, 5.39–138.27) for acute appendicitis vs 18.87 μmol/L (range, 2.27–120.59) for other diagnosis group (P = .038). The sensitivity and specificity of urinary 5-HIAA at a cutoff value of 19 μmol/L were 71% and 50%, respectively. Receiver operating characteristic analysis showed that the area under curve was 0.64 (confidence interval [CI], 0.513–0.737) for urinary 5-HIAA, which was lower than white blood cell count (0.69; CI, 0.574–0.797), neutrophil count (0.68; CI, 0.565–0.792), and C-reactive protein (0.76; CI, 0.657–0.857). There was no significant difference in the median values of 5-HIAA between different grades of severity of appendicitis (P = .704).

**Conclusion:** Urinary 5-HIAA is not an ideal test for the diagnosis of acute appendicitis.

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## 1. Introduction

Acute appendicitis is one of the most common surgical emergencies, especially in children and young adults [1,2]. Seven percent of the population will develop appendicitis at some point during their lifetime [1]. This condition is treated urgently because progression of the disease leads to life-threatening complications such as sepsis, perforation, and peritonitis [3,4]. The standard treatment of appendicitis is appendectomy.

The diagnosis of appendicitis is difficult, and only half of the cases are correctly identified [5]. The Alvarado scoring system, based on clinical observations and biochemistry measurements, has been used to aid in diagnosis of appendicitis [6]. However, the presenting signs and symptoms vary according to the position of appendix, and nonclassical symptoms are common [7]. Many patients undergo unnecessary appendectomy and are found to have a normal appendix [8]. Computed tomographic (CT) imaging has high sensitivity, but it exposes children and women of childbearing age to extensive ionizing radiation [9]. Ultrasound is associated with low sensitivity and specificity [9,10].

Previous studies have indicated that appendix is enriched with enterochromaffin cells [11]. These cells are densely concentrated with serotonin. Ninety-five percent of serotonin is secreted from enterochromaffin cells in the gut [11]. In addition, lamina propria of appendix also contains enterochromaffin cells secreting serotonin. Once serotonin is secreted in the system, 90% is metabolized in the liver; and the remaining, in lung and kidney. 5-Hydroxyindoleacetic acid (5-HIAA) is the main metabolite of serotonin and mainly discarded in the urine [12].

High levels of serotonin and 5-HIAA are associated with appendicular pathology [12]. Induced appendicitis in rabbits causes a significant rise in 5-HIAA compared to controls [12]. There is growing evidence to suggest the use of spot urinary 5-HIAA test to diagnose appendicitis [13]. The aim of our study was to establish whether urinary 5-HIAA could be used as an effective diagnostic test for appendicitis. Our second objective was to determine if there was an association between urinary 5-HIAA and the degree of inflammation of appendicitis based on histopathologic grading and Alvarado score.

## 2. Methods

## 2.1. Participants

This was a double-blinded prospective study conducted from December 2014 to October 2015 at the emergency surgical unit in a

☆ Funding: The research project was funded by National Health Service Tayside and University of Dundee Medical School, Dundee, UK.

☆☆ Conflict of interest: None declared.

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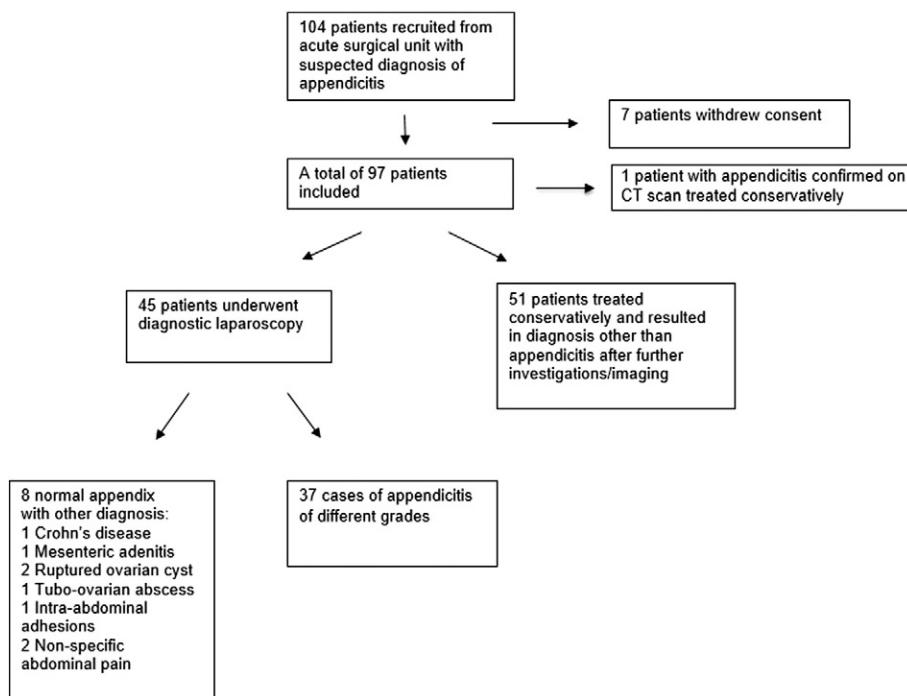


Fig. 1. Patient recruitment to study groups and their final diagnosis.

large teaching hospital. All patients admitted with right iliac fossa pain and presumptive diagnosis of acute appendicitis were asked to participate in the study. Patients were excluded if they were taking drugs interfering with serotonin levels, such as, monoamine oxidase inhibitors, serotonin and norepinephrine reuptake inhibitors, and Lithium. Medical and drug history was noted. Patient consent to participate was obtained once the patient had received initial treatment, and necessary blood and urine tests were taken. The urine samples were collected within 24 hours of the time of admission and before any surgery was performed. The ethical approval to conduct the study was obtained from National Ethics Committee, Health Research Authority UK.

## 2.2. Samples

Once collected, the urine samples were acidified by 12 N HCl and stored at  $-70^{\circ}\text{C}$ . Samples were analyzed using enzyme-linked immunosorbent assay technique. The sample analysis was conducted on ALPCO 5-HIAA enzyme-linked immunosorbent assay. When compared to high-performance liquid chromatography, its methodology has shown strong correlation ( $r = 0.99$ ;  $n = 47$ ). The sample size of 35 patients was estimated [11] to provide sensitivity of 98% with confidence interval (CI) of 95% and accuracy of 0.05% for urinary 5-HIAA.

Other diagnostic tests used to aid in diagnosis of acute appendicitis were also recorded: white cell count (WCC), neutrophil count, C-reactive protein (CRP), and Alvarado score. Alvarado score is based on clinical observations and biochemistry measurements and ranges from 1 to 10; a score of 5 or 6 is suggestive of appendicitis, whereas score of more than 7 indicates high probability of acute appendicitis.

## 2.3. Data analysis

Medical information was retrieved from the admission records. This included patient's presenting complaint, duration of symptoms, age, medical history, current medications, and final diagnosis. Results from hematological and biochemical tests along with histopathology reports were acquired from electronic medical records.

Grading of acute appendicitis was based on the same staging system used in earlier studies [11,14]. The categories of acute appendicitis were

mild acute appendicitis, acute appendicitis with peritonitis/perforation, acute necrotising appendicitis, and acute gangrenous appendicitis [11,14].

SPSS version 22 program was used to perform statistical analysis. A descriptive analysis was obtained for patients included in the study. Shapiro-Wilk test was conducted to check for normal distribution of dependent variables, such as urinary 5-HIAA, WCC, neutrophil count, CRP, and Alvarado score ( $P < .001$ ). It showed that the data were nonparametric. Mann-Whitney  $U$  test and Kruskal-Wallis test were used for comparison of 2 and more than 2 groups, respectively. Receiver operating characteristic (ROC) curve was used to plot graph for sensitivity and specificity of urinary 5-HIAA test and other diagnostic tests. For patients who underwent laparoscopy and appendectomy, intraoperative findings and histopathology of specimen were used as criterion standard tests to check diagnostic accuracy of urinary 5-HIAA and other biochemistry tests; however, for those who did not have an operation, CT scan was used. To measure sensitivity and specificity of combination of more than 2 diagnostic tests, binary logistic regression analysis was performed, and the combined predictive score derived from it was used to generate ROC curve [15]. The graph of ROC was plotted for sensitivity against specificity, and the area under curve (AUC) was calculated. It measured the probability of correctly diagnosing a patient in a test group. The value of AUC ranged from 0.5 to 1.0. The ability of diagnostic test to identify patients with appendicitis was considered optimal as AUC value reached closer to 1.0.

Table 1  
Comparison of mean values of different diagnostic tests in 2 groups

|                                             | Final diagnosis |             |                    |             |       |
|---------------------------------------------|-----------------|-------------|--------------------|-------------|-------|
|                                             | Other diagnosis |             | Acute appendicitis |             | P     |
|                                             | Median          | Range       | Median             | Range       |       |
| 5-HIAA ( $\mu\text{mol/L}$ )                | 18.87           | 2.27-120.59 | 24.19.             | 5.29-138.27 | .038  |
| WCC ( $\times 10^9/\text{L}$ )              | 9.50            | 5.20-20.20  | 12.50              | 3.80-23.90  | .002  |
| Neutrophil count ( $\times 10^9/\text{L}$ ) | 6.25            | 3.40-17.10  | 10.55              | 1.80-20.90  | .002  |
| CRP (mg/L)                                  | 4.00            | 4.00-334.00 | 38.00              | 4.00-434.00 | <.001 |

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