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RESEARCH ARTICLE
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A COMPARATIVE STUDY ON ROLE OF METRONIDAZOLE IN SURGICAL MANAGEMENT OF ACUTE SIMPLE VERSUS ACUTE COMPLICATED APPENDICITIS

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Abstract

Background: Although appendicectomy remains the standard and classical treatment for acute appendicitis, Metronidazole plays an important role in addition to antibiotics in controlling the infection was tested as an effective protocol. But comparison of its role in acute simple versus acute complicated Appendicitis was attempted in this study.

Aim of the study: To assess the effectiveness and outcomes of Metronidazole as an adjuvant to antibiotic treatment for acute simple and acute complicated appendicitis.

Materials: This was a prospective, controlled, non-randomized study involving 76 patients aged between 18 and 54 years. All clinically diagnosed with acute and acute complicated appendicitis. These patients were treated with appendicectomy and Metronidazole and antibiotic therapy, which included Metronidazole 500 mg IV thrice daily in addition to Ceftriaxone 1 gram twice daily administered three times daily for one week. Once the clinical improvement was observed, the treatment was switched to oral Metronidazole 200 mg thrice daily along with Cefixime 200 mg twice daily for 5 to 7 days. All the data related to the patients was analyzed using suitable statistical methods.

Results: Antibiotic treatment with Metronidazole was successful and feasible in 68/76 (89.74%) patients. In Group 'A' 22/38 patients (57.89%) sought medical attention within 24 hours of symptom onset, 10/38 patients (26.31%) presented between 24 and 48 hours. In group B 16/38 patients (42.10%) sought medical attention within 24 hours of symptom onset, 10/38 patients (26.31%) presented between 24 and 48 hours. There was statistical significance on Chi square test on the time of reporting to EMD and Alvarado score with p value 0.001 (p significant at less than 0.05).

Conclusion: Metronidazole for acute simple and acute complicated Appendicitis was safe, feasible, and effective option.

Introduction

Acute appendicitis is the most common emergency in general surgical practice worldwide, with a lifetime incidence estimated at one in ten individuals. (1) For decades, appendicectomy has been the standard and preferred surgical procedure to prevent the progressive inflammation that can ultimately lead to perforation. (2) However, recent findings suggest that the progressive nature of acute appendicitis and its subsequent perforation are relatively rare, particularly in young and adult patients. In fact, most cases are simple and uncomplicated. (3) In light of these findings, there has been increasing discussion about the potential role of Metronidazole in conservative acute simple and acute complicated appendicitis used along with antibiotics and supportive measures. Surgical management has long been established for Appendicitis but usage of antibiotics and Metronidazole was the choice of the surgeons. (4) While appendicectomy is generally considered a safe and straightforward procedure, it can lead to complications, including wound infection, pelvic abscess, and bowel obstruction due to adhesions, pneumonia, and entero-cutaneous fistula. (5) In recent years, there has been growing evidence supporting the use of primary antibiotic therapy along with Metronidazole for select patients with complicated acute appendicitis. (6) Despite this trend, the effectiveness, safety, and outcomes of Metronidazole as a part of protocol in Appendicectomy and comparison of its role in acute appendicitis and complicated acute appendicitis conservative management remain subjects of debate, and no clear consensus has been reached. (7) The primary goal of this study is to evaluate the effectiveness and feasibility of using Metronidazole along with antibiotics as the sole treatment for simple, appendicitis and complicated acute appendicitis focusing on short- and long-term outcomes, complications, hospital stay length, sick leave, and overall treatment efficacy.

Materials

This prospective controlled study was conducted at a major hospital between January 2022 and December 2023, involving 76 patients aged 18 to 54 years, all presenting with a clinical diagnosis of acute uncomplicated appendicitis. An ethics committee of the Institute had approved the study and a protocol approved by the committee was used in the study.

Inclusion Criteria: Patients aged between 18 and 54 years were included. Patients with all the features of acute appendicitis and acute appendicitis with complications were included. Patients willing to participate in the study were included. Patients of both the genders were included. Patients with severe acute complicated appendicitis, such as perforation, abscess, or localized or diffuse peritonitis were included.

Exclusion Criteria: Patients, who refused conservative treatment and opted for surgery, as well as those with a positive pregnancy test, were excluded. Patients with co-morbidities such as diabetes, congenital hemolytic anemia, hypertension, low immunity, or a history of antibiotic allergies were excluded. Informed written consent was obtained from all participants was taken. A total of 76 patients diagnosed with acute appendicitis diagnosis were included in the present study. The patients were divided into two groups. Group A consisted of Acute simple Appendicitis and Group B consisted of acute complicated Appendicitis. The diagnosis of acute appendicitis was based on a detailed history of mild to moderate right lower abdominal pain, accompanied by nausea and anorexia, as well as a careful clinical examination revealing localized and rebound tenderness in the right iliac fossa. The definitive diagnosis was confirmed through laboratory blood tests, including a complete blood count (CBC) and C-reactive protein (CRP), along with imaging studies (ultrasound and CT scan), which were performed for all patients enrolled in the study. The Alvarado scores for all patients were recorded to ensure an accurate diagnosis **(Table 1).** A pregnancy test was conducted for all female patients. The treatment approach was fully explained to each patient, and written informed consent was obtained. Elevated blood inflammatory markers (WBCs, neutrophilia, and elevated CRP), and imaging, primarily high-resolution ultrasound or CT scan were considered as supportive to the diagnosis of acute complicated appendicitis.

Protocol of treatment followed in the study: All patients included in the study were admitted to the surgical ward, placed on a nil-by-mouth regimen, and started on intravenous fluids. They then received par-enteral antibiotics, including ceftriaxone 1 gram twice daily and Metronidazole 500 mg in 100 ml, administered three times daily for 48 to 72 hours. Patients were monitored regularly with 12-hourly charts documenting vital signs and any changes in localized abdominal symptoms. For patients allergic to cephalosporin, intravenous ciprofloxacin 400 mg twice daily were used. Patients who showed clinical improvement and were stable upon investigation were discharged on oral antibiotics (cefixime 400 mg twice daily or ciprofloxacin 500 mg three times daily, along with Metronidazole 500 mg three times daily) for a duration of 7 to 10 days, with follow-up appointments scheduled for further evaluation. During the hospital stay, patients whose symptoms showed no improvement or worsened underwent appendicectomy.

TABLE 1: Alvarado score for diagnosis of acute appendicitis

Feature	Score
Migratory pain	1
Anorexia	1
Nausea	1
Tenderness in right lower quadrant	2
Rebound pain	1
Elevated temperature	1
Leukocytosis	2
Shift of white blood cells count to the left	1
Total	10

(Alvarado score: 0–4: unlikely appendicitis; 5-6: equivocal for appendicitis; 7-8: probably appendicitis; 9-10: most likely appendicitis (Table 1 is from Neupane et al. [5] under the Creative Commons Attribution License/Public Domain).

Patients who responded successfully to conservative treatment were instructed to return if their initial symptoms recurred. All patients who received conservative treatment were followed up for a period of 6 to 12 months. The primary objectives of this study were to evaluate the feasibility and outcomes of Metronidazole antibiotic-based post surgical treatment for acute simple and acute complicated appendicectomy. The main endpoint of the study was to determine the number of patients who experienced a successful, complication-free conservative treatment, defined as being discharged from the hospital after complete resolution of their signs and symptoms, with no need for appendicectomy and no recurrence of symptoms during the follow-up period in both the groups.

The secondary endpoints included The final outcome of the effect of Metronidazole on acute simple versus acute complicated appendicitis was observed in terms of tolerance for pain during the post operative period, recurrence of symptoms complications, Hospital stay, subsequent surgery required and 06 months follow up in terms of prolonged leave, subjective feeling of the patients expressed as fair, good and very good were recorded. Data analysis was performed using IBM SPSS version 22. The Chi-square test was applied to assess the significance of associations between variables, with a p-value of <0.05 considered statistically significant.

Results

A total of 76 patients diagnosed with acute appendicitis diagnosis were included in the present study. Group A consisted of acute simple Appendicitis patients and Group B consisted of acute complicated Appendicitis patients. Group 'A' patients (Acute simple Appendicitis) were 38 in number. Of the 38 patients of Group A, 27 were male (71.05%) and 11/51 were female (28.94%), with a male to female ratio of 2.45:1. The highest incidence of simple acute appendicitis was observed in the age groups 21 to 30 years; 13/38 (34.21%), followed by 16 to 20 years with 10/38 (26.31%) patients. 09 (23.68%) patients were in the age group of 31 to 40 years **(Table 2).** Of the 38 of Group B patients, 25 were male (65.78%) and 13/51 were female (34.21%), with a male to female ratio of 1.92:1. The highest incidence of complicated acute appendicitis was observed in the age groups 21 to 30 years; 17/38 (44.73%), followed by 31 to 40 years with 11/38 (28.94%) patients. 07 (18.42%) patients were in the age group of 16 to 20 years **(Table 2).** The incidence was similar in both the groups A and B and there was no statistical significance with p value more than 0.05.

Table 2: Showing the Age and gender incidence in the study subject (n-76: Group A-38 Group-B-38)

Observation	Acute Simple Appendicitis	Acute complicated Appendicitis	**P value**
Age Interval 16–20	10- 26.31%	07- 18.42%	0.063
21–30	13- 34.21%	17- 44.73%	
31–40	09- 23.68%	11- 28.94%	
41–50	04- 10.52%	02- 05.26%	
51–60	02- 05.26%	01- 02.63%	
Males	27- 71.05%	23- 60.52%	
Females	11- 28.94%	15- 39.47%	

In terms of patient presentation to the Emergency Department (EMD) of the Hospital, in Group 'A' 22/38 patients (57.89%) sought medical attention within 24 hours of symptom onset, 10/38 patients (26.31%) presented between 24 and 48 hours, and 06/38 patients (15.78%) arrived within 48 to 72 hours **(Table 3).** In group B 16/38 patients (42.10%) sought medical attention within 24 hours of symptom onset, 10/38 patients (26.31%) presented between 24 and 48 hours, and 06/38 patients (15.78%) arrived within 48 to 72 hours **(Table 3).** There was statistical significance on Chi square test on the time of reporting to EMD and Alvarado score with p value 0.001 (p significant at less than 0.05), **(Table 3).**

Table 3: Showing the duration before reporting to the EMD and Positive mean Alvarado score in the study (n-76: Group A-38; Group-B-38)

Duration of Symptoms in Hours	Simple Appendicitis	Acute complicated Appendicitis	P value
≤24	22- 57.89%	16- 42.10%	**0.001**
24–48	10- 26.31%	13- 34.21%	
48–72	06- 15.78%	09- 23.68%	
Mean Alvarado score	06	09	

The diagnosis of acute uncomplicated appendicitis was based on patient history, clinical examination, laboratory investigations—primarily inflammatory markers (leukocytosis, neutrophilia, and C-reactive protein)—and imaging. Ultrasound was performed on all patients, while CT scans were conducted only for cases where the diagnosis was uncertain (27 patients), **(Table 4)** It was observed that the Laboratory investigations and radiological investigations were more prominent and conclusive in acute complicated appendicitis when compared to acute simple appendicitis. The chi square test was significant with p value less than 0.05. **(Table 4)**

Table 4: Showing the Positive Laboratory and Radiological investigations in the study (n-76: Group A-38; Group-B-38)

Observation	Number	Percentage	P value
Leukocytosis			
Acute simple Appendicitis	15	39.47	
Acute complicated Appendicitis	26	68.42	
Neutrophilia			
Acute simple Appendicitis	10	26.31	
Acute complicated Appendicitis	25	65.78	
C reactive protein			0.001
Acute simple Appendicitis	11	28.94	
Acute complicated Appendicitis	24	63.15	
Ultra sound Abdomen			
Acute simple Appendicitis	23	63.15	
Acute complicated Appendicitis	27	71.05	
CT scan Abdomen- 27			
Acute simple Appendicitis	10	26.31	
Acute complicated Appendicitis	16	42.10	

The final outcome of the effect of Metronidazole on acute simple versus acute complicated appendicitis was observed in terms of tolerance for pain during the post operative period, recurrence of symptoms complications, Hospital stay, subsequent surgery required and 06 months follow up in terms of prolonged leave, subjective feeling of the patients expressed as fair, good and very good were recorded. All the data was tabulated in the **Table 5.** It was noted that the tolerance for pain during the post operative period (p-0.001), recurrence of symptoms (0.01), subsequent surgery required (0.01) and 06 months follow up in terms of prolonged leave, subjective feeling of the patients expressed as fair, good and very good (0.01) were statistically significant factors in both the groups (p significant at <0.05), **(Table 5).**

Table 5: Showing the Final outcome indicators presented by both groups patients (n-76: Group A-38; Group-B-38)

Observation	Acute Simple Appendicitis	Acute complicated Appendicitis	P value
Effectiveness of Antibiotic and Metronidazole	38	30	0.001
Tolerance to Pain level- VAS score			
1 to 4	25- 65.78	18- 47.36	0.001
5 to 7	12- 31.57	17- 44.73	
8 to 10	01- 02.63	03- 07.89	
Recurrence of symptoms			0.01
Absent	36- 94.73	30- 78.94	
Present	02- 02.63	08- 21.05	
Complication			
Abscess formation	02- 02.63	04- 10.52	0.211
Wound infection	01- 02.63	03- 07.89	
Fistulae	01- 02.63	02- 02.63	
Chronic pain	03- 07.89	05- 13.15	
Hospital Stay			
05 to 07 Days	36- 94.73	21-55.26	0.533
08 to 10 days	01- 02 63	10- 26.31	
More than 10 days	00- 00	08- 21.05	

Subsequent surgery			
Required	01- 02.63	04- 10.52	0.001
Not- required	37- 97.36	34- 89.47	
06 months follow up results			
Prolonged Medical leave	02- 02.63	06- 15.78	0.01
Satisfactory	09- 23.68	10- 10.52	
Good	25- 65.78	18- 47.36	
Very good	02- 02.63	04- 10.52	

Discussion: Acute simple appendicitis is a common condition with an estimated incidence of approximately one in ten people over their lifetime. The majority of cases present as simple but acute complicated appendicitis presents with perforation, appendicular mass, appendicitis with high grade fever, vomiting and paralytic ileus (2, 4). It was traditionally believed that acute appendicitis followed a progressive course, potentially leading to perforation and either localized or diffuse peritonitis if not treated within a proper timeframe (6, 7). However, this progression was found to be relatively rare. While appendicectomy has long been considered the gold-standard treatment, the procedure carries significant short-term and long-term complications, including wound infections, entero-cutaneous fistulas, and adhesive small bowel obstructions. Therefore, several studies have recently proposed conservative antibiotic treatment combined with Metronidazole as a primary protocol during the post operative period of appendicectomy. (6, 8 to 12) In the present study a total of 76 patients diagnosed with acute appendicitis diagnosis were included in the present study. Group A consisted of acute simple Appendicitis patients and Group B consisted of acute complicated Appendicitis patients. Group A patients (Acute simple Appendicitis) were 38 in number. Of the 38 patients of Group A, 27 were male (71.05%) and 11/51 were female (28.94%), with a male to female ratio of 2.45:1. The highest incidence of simple acute appendicitis was observed in the age groups 21 to 30 years; 13/38 (34.21%), followed by 16 to 20 years with 10/38 (26.31%) patients. 09 (23.68%) patients were in the age group of 31 to 40 years **(Table 2).** Of the 38 of Group B patients, 25 were male (65.78%) and 13/51 were female (34.21%), with a male to female ratio of 1.92:1. The highest incidence of complicated acute appendicitis was observed in the age groups 21 to 30 years; 17/38 (44.73%), followed by 31 to 40 years with 11/38 (28.94%) patients. 07 (18.42%) patients were in the age group of 16 to 20 years **(Table 2).** The incidence was similar in both the groups A and B and there was no statistical significance with p value more than 0.05. With advances in preoperative diagnostics, particularly improvements in imaging techniques such as high-resolution ultrasound and abdominal CT scans, the diagnosis of simple, uncomplicated acute appendicitis can now be made with greater confidence. (13) Recently, there has been a growing trend toward postoperative treatment with Metronidazole for all types of Appendicitis cases during the post operative period. (14) It is based on various patho-physiological and radiological evidences found on review of the literature. (15). It was also reported by few authors that the usage of Metronidazole IV over a period of 7 days in addition to antibiotics has reduced the chances of sick leave, hospital stay duration, and the cost of treatment when compared to only antibiotics appendectomy. (16) However, some challenges remain, including the risk of recurrent disease (up to 35%), lack of definitive histo-pathological confirmation, and the potential for increased antibiotic resistance and Clostridium difficile infections. (17) Several factors present at admission are considered independent predictors of successful conservative treatment for acute simple appendicitis and acute complicated appendicitis patients. They include a High-grade fever, High C-reactive protein levels, a modified Alvarado score more than 8. (18) On radiological imaging a larger size and diameter of appendix with an appendicolith. Additionally, patients with a shorter duration of symptoms and presenting with above signs indicate rapid progression of disease. (20) Tools like the Adult Appendicitis Score (AAS), modified Alvarado score, and Appendicitis Inflammatory Response (AIR) score are cost-effective methods to reduce the negative appendectomy rate. (21) These scoring systems can stratify patients into high-risk groups with a specificity of up to 94%. (22) A

significant concern regarding the long-term outcome of complicated acute appendicitis was the potential for recurrence. (23) In the present study, the recurrence rate during the 6 was 08/38 (21.05%). All recurrent cases were uncomplicated, with no evidence of perforation or abscess, and they were successfully treated with appendicectomy, without complications or mortality. Lundholm et al. (24) reported that the long-term relapse rate after using Metronidazole during the postoperative period was approximately 15%, suggesting that combination of antibiotics and Metronidazole could provide an overall benefit of 60–70% over a 10-year follow-up period. McCutcheon et al. [26] and Tanaka et al. [27] observed recurrence rates of 4.4% and 28.6%, respectively. Similarly, a study by Salminen et al. [28] found that the rate of late recurrence among patients initially treated with antibiotics and Metronidazole within 5 years was 39.1%. These findings support the viability of Postoperative Metronidazole and antibiotic therapy as a best choice during post appendicectomy period.

Conclusions

Metronidazole for acute simple and acute complicated Appendicitis was safe, feasible, and effective option.

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