ORIGINAL ARTICLE

Comparative Study of Single Dose Per-operative Metronidazole versus Multiple Doses Postoperative Metronidazole in Acute Non-Complicated Appendicitis: A View on Postoperative Complications

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Abstract:

Background: It has now been proved by researches that per-operative single dose prophylactic antibiotics more crucial in preventing postoperative wound infection in elective cases and clean-contaminated cases like acutely inflamed non-perforated appendicitis. *Aim and Objectives*: This study investigated the effect of a single dose of metronidazole infusion per-operatively in the treatment of patients undergoing appendicectomy regarding postoperative infective complications. *Material and Methods*: A total number of 111 patients of non-complicated (suppurative and catarrhal) appendicitis enrolled in this prospective study between October 2015 and October 2017. Patients were allocated to two groups in a randomized way. Fifty-one patients in Group A were given a single dose of metronidazole per-operatively. Sixty patients in Group B were given multiple doses of metronidazole postoperatively. Postoperative fever, wound infection, seroma, and intrabdominal collections were compared between both groups. Statistical analysis was performed using Student's t-test and Chi-square test. *Results*: The patients of both groups were similar in baseline characteristics. No significant difference was found in the rate of postoperative fever and wound infection in both groups. In Group A there were five patients (9%) developed postoperative fever, four of them (7.8%) because of wound infection. In Group B there were six patients (10%) developed postoperative fever, four of them (6.7%) because of wound infection. None of the patients developed seroma or intraabdominal abscesses. *Conclusion*: Single per-operative dose of metronidazole is quite effective in reducing the incidence of postoperative fever and wound infection after appendicectomy.

Keywords: Appendicitis, Appendicectomy, Wound infection, Postoperative fever, Metronidazole

Introduction:

Appendicitis is the most common cause of acute abdominal pain necessitates surgical intervention. The lifetime risk of the population for developing acute appendicitis may reach up to 20% [1, 2]. Appendicectomy is the most frequently performed emergency operation. Cases of non-perforated appendicitis are regarded as clean-contaminated surgical cases. However, without antibiotics, the rate of wound infection has been reported to be between 10%-40% after appendicectomy [3, 4]. Hence, prophylactic antibiotics are recommended [4].

Metronidazole is an antibiotic and antiprotozoal medication, and it is used either alone or with other medicines to treat acute appendicitis. It is effective against infections caused by anaerobic organisms mainly Bacteroids which is the main organisms

isolated in acute appendicitis. Metronidazole has been shown to be useful in appendicitis given as a single intravenous dose of 500 mg, but it will be more effective in providing a current level at the time of wound contamination [5].

Even in the uncomplicated nonperforated appendicitis, the administration of both per-operative and postoperative antibiotics can increase the economic burden and encourage the appearance of resistant microorganisms [6]. Studies on the role of single dose per-operative antibiotics without postoperative antibiotics in appendicectomy are controversial.

Therefore, this study was achieved in patients with uncomplicated nonperforated acute appendicitis to evaluate the efficacy of a single dose of per-operative metronidazole versus both per-operative and postoperative metronidazole in aiming to minimize the post-surgery infective complications.

Material and Methods:

Study design and setting

This was a prospective comparative study done at Al-Kindy Teaching Hospital in the general surgery department from October 2015 to October 2017.

Inclusion criteria and study sample

Patients who had been included in the study should fulfill these requirements: Age distribution between 15 – 45 years old, the inflamed appendix should be proved suppurative macroscopically during operation by the operator, i.e., perforated and gangrenous appendix were not included in this study, catarrhal appendix proved by sending the excised appendix for histopathological examination postoperatively. Appendicectomy should be done by the same surgical team to reduce the possibility of bias. Appendicectomy should be done by gridiron incision. The Body Mass Index (BMI) should be less than 30.

Exclusion criteria

Female subjects who were pregnant, a patient receiving antibiotics within 72 hr of admission, patients with diabetes mellitus, uremia, steroid therapy, patients who have a local or generalized infection before surgery, and patients with drug allergy, all were excluded from this study.

Assignment and protocol

Clinical diagnosis of acute appendicitis was made after taking a good history and performed a proper physical examination. All necessary investigations were done including abdominal and pelvic ultrasound or computerized tomography scan if needed. A format for every patient had been completed, and all patients should fit the inclusion and exclusion criteria for this study.

All essential standardized strategy of aseptic safety measures in the surgical theater were followed. The standard operation technique was performed in open appendicectomy through the right lower quadrant incision.

By opening sealed envelopes, the patients with nonperforated inflamed appendix diagnosed intraoperatively were allocated into two groups in a randomized method. Group A was given only a single dose of metronidazole vial 500 mg per-operatively at time of incision by intravenous infusion route at an approximate rate of 5 ml/min, i.e., 20 minutes' duration (total dose). Group B was given multiple doses of metronidazole started per-operatively (500 mg/ 8 hourly intravenously) then continued for three days postoperatively. No additional antibiotics were offered for both groups. All specimens of the excised appendices were sent for histopathological assessment.

Patients were regularly observed in the postoperative time. Temperature chart was preserved. The temperature was considered significant if it exceeds 38°C. The wound dressing was checked after two days and examined it thoroughly for any marks of wound site infection as assigned by the Centers for Disease Control and Prevention (CDC) [7]. These marks are local edema, erythema, local tenderness, fever or discharging pus. The intraabdominal collection was identified as any fluid gathering within the abdominal cavity seen by sonography or CT examination. Patients were released from the hospital when they were non-febrile, had no marks of wound infection, wholly mobilized, could start an oral fluid diet with real bowel sound, and had satisfactory pain relief with oral analgesics. They should stay in hospital surgical ward for at least (3-5) days postoperatively. After discharging of the patient, follow up was continued and the suture was removed on the 7th or 8th postoperative day. Swab for culture and sensitivity was sent to a microbiology lab in cases of wound infection. More follow up was made in all cases for at least ten days postoperatively. Those patients who were not attending the outpatient department for follow up were excluded from the study.

Ethical consideration

This study was conducted under the Declaration of Helsinki and was approved by the hospital's ethics and scientific research committee (registration code: 38/2015). Informed consent was taken from all the patients involved in the study, and their personal health information was safeguarded.

Statistical analysis

Descriptive statistics were first used to record data and presented as a mean and standard deviation. To compare the continuous variables, Student's t-test was used. Chi-square test was applied to find out associations between related categorical variables. All statistical analyses were achieved in SPSS software (IBM SPSS Statistics for Windows, version 22.0 Armonk, NY, USA). A *P*-value < 0.05 was regarded to be significant.

Results:

During the study period, 164 patients with acute appendicitis were enrolled. Thirty-two patients were excluded preoperatively from the study sample because of the previously mentioned exclusion criteria. Out of the 132 patients underwent appendicectomy, 123 patients were proved to have nonperforated appendicitis, and they randomly allocated. Another 12 patients were excluded because they either withdrew from the study, had another diagnosis on final histopathological examination, or not attended for follow up. Finally, 111 patients met the inclusion criteria of the study and were subjected to statistical analysis (Fig. 1). Among these, 70 (63.1%) were male, 41 (36.9%) were female, with a male/female ratio of (7:4). Patients ranged in age from 15 to 45 years with a mean of 23.9 years. The results between the two groups; Group A with 51 patients and Group B with 60 patients, were compared regarding postoperative reading in temperature and infective wound complications.

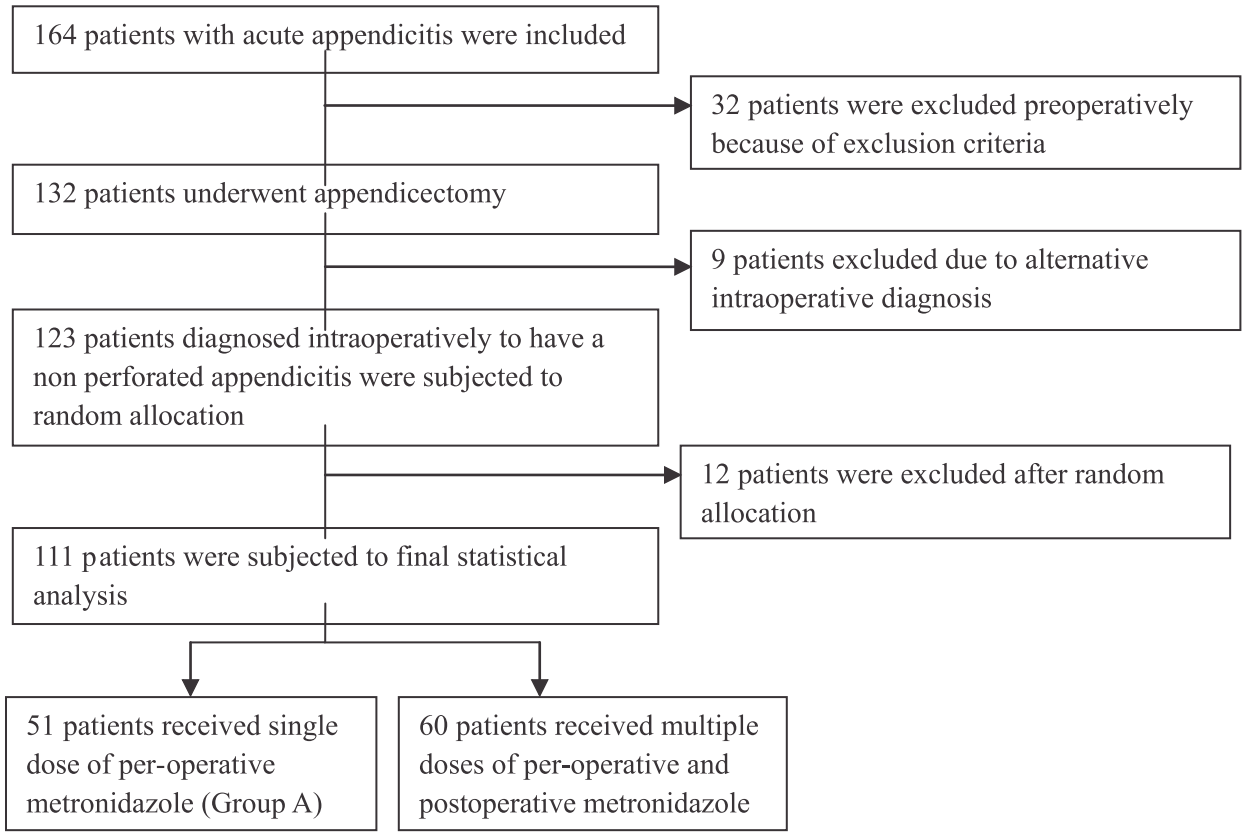

Fig. 1: Flowchart of the Study's Patient

Table 1: Patient Demographics and Body Mass Index

Characteristic	Group A (n=51)	Group B (n=60)	Total (n=111)	P value
Age (in years)	23.1 ± 3.2	24.5 ± 2.2	23.9 ± 2.4	0.096*
Gender (male: female)	32 (63):19 (37)	38 (63):22 (37)	70 (63.1):41 (36.9)	0.122†
Body mass index (kg/m2)	23.8 ± 1.0	24.1 ± 1.8	23.9 ± 1.4	0.598*

*Values are presented as Mean± Standard Deviation or number (%). Group A: per-operative single dose metronidazole. Group B: per-operative and postoperative metronidazole. *Student's t-test; †Chi-square test.*

Table 2: Comparison of Infective Complications

Complication	Group A (n=51)	Group B (n=60)	Total (n=111)	P value †
Postoperative fever	5 (9.8)	6 (10.0)	11 (9.9)	0.210
Superficial wound site infection	4 (7.8)	4 (6.7)	8 (7.2)	0.466
Deep wound site infection	0	0	0	0
Seroma	0	0	0	0
Intraabdominal abscess	0	0	0	0

Values are presented as number (%). Group A: per-operative single dose metronidazole. Group B: per-operative and postoperative metronidazole. †Chi-square test

Table 1 shows patients' BMI and demographics. Both groups were comparable, and there were no significant differences in term of age (p= 0.096), gender (p=0.122), and BMI (p=0.598).

Regarding postoperative body temperature measurements which exceed 38°C, there was no significant difference between the two groups; 5 patients (9.8%) in Group A vs. six patients (10%) in Group B; p=0.210. Four of those patients of Group A who developed fever was due to postoperative wound infection while the 5th patient who had 39°C fever was due to a chest infection. In Group B, postoperative wound infection was the cause of fever in 4 patients; the other two patients had a fever because of urinary tract infection and thrombophlebitis at the site of the cannula.

The rate of wound site infection in Group A was 7.8% and in Group B was 6.7% and the difference was not statistically significant (p=0.466).

All the patients with wound infection were superficial wound site infections detected on 3rd - 7th postoperative day and managed by daily normal saline dressings, swab for culture and sensitivity was sent, and empirical treatment was given with antibiotics. During 4-6 days, wound infection in all patients was disappeared and healed by secondary intention. No seroma, deep wound site infection or intraabdominal collections was encountered in this study (Table 2).

Discussion:

Wound site infection is the most frequently encountered complication after appendicectomy [3, 4]. The suitable period of antimicrobial administration for the avoidance of postoperative surgical wound infection has remained a topic of debate. When a prophylactic antibiotic is given at a proper time and dose before incision, it may be useful as the therapeutic tissue levels are attained at this situation [4].

Single-dose antimicrobial prophylaxis for major surgery is a widely accepted principle. Recommendations have been based on laboratory studies and numerous clinical trials published in the literature. However, in practice, single-dose prophylaxis has not been universally accepted, and multiple-dose regimens are still used in some centers.

While several studies suggested prophylactic antibiotics in nonperforated appendicitis, only a few reviews reported that a single dose of preoperative antimicrobials could lessen surgical wound infection [2, 6, 8-10].

Our study included 111 patients, all with acutely inflamed non-complicated appendicitis. It was used only single dose per-operative antibiotic (metronidazole) against anaerobic organisms in a group of patients and compared it with another group of patients who received multiple doses of the same medicine and observed them for wound infection postoperatively. It was encountered only four patients with wound infection in both groups. No statistically significant difference in the rate of wound site infection between Group A and Group B was found in our study. The infection rate was about 7.2% in both groups. Comparing with Group B, we noticed fewer burdens on our patients (Group A) in term of purchasing antibiotics and less antibiotic-associated side effects like post-operative nausea, vomiting, and diarrhea. It is also hope that this act would have helped toward a decrease in antibiotic resistance.

One thing which needs particular emphasis is that theatre etiquettes and sterilization techniques should be considered at any infection introduced as the breach of sterility can be falsely attributed to the non-use of post-operative antibiotics. In our series, we took special care to avoid any violation of sterility in the theatre.

The result of our study was comparable with other studies conducted nationally by Saad *et al*. [11] as well as internationally by Busttil *et al*. [12] and Winslow *et al*. [13], they all concluded with the observation that adding post-operative broad-spectrum antibiotics only added financial burden and side effects and had no impact towards preventing wound infection.

Wound infection rate was not significantly different with the results in a study done by Culver *et al*. [14] as it was (8.1%) in patients given a single per-operative dose of metronidazole and (7.9%) in the patient receiving multiple doses of it postoperatively.

The results of our study were differ from other research done by Sevin *et al.* [15] as they reported opposite results showing that postoperative metronidazole for 3 days is superior to single dose per-operatively possibly due to the variety in patients included regarding comorbidity factors (diabetes mellitus, uremia, etc.), also because of inclusion of all types of appendicitis.

Our study was comparable to a study done in Deep South Centre for Effectiveness Research, Birmingham, USA it was concluded that single per-operative metronidazole is quite enough to reduce postoperative wound infection in acute suppurative appendicitis [16].

In our work, when compared to a single dose per-operative metronidazole only, postoperative metronidazole in adding to per-operative metronidazole did not demonstrate any extra benefit in dropping wound infection. Hence, prophylactic administration of single dose per-operative metronidazole without any additional postoperative metronidazole could be ideal in uncomplicated nonperforated appendicitis.

Moreover, our results are further strengthened by the recent studies reported that the postoperative antibiotic administration was not beneficial in nonperforated appendicitis as it not reduce infectious complications but could increase antimicrobial resistance and cost of care [6, 8, 17, 18].

However, this study has a limitation as the population sample was relatively small; hence

further large-scale studies are desired to set up a typical protocol for antibiotic usage.

Conclusion:

A single per-operative dose of metronidazole during the riskiest period of bacterial contamination is quite effective in reducing the incidence of wound infection after excision of the uncomplicated acutely inflamed appendix. It is more economical and safe regimen. The administration of postoperative metronidazole would not be essential in this condition.

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