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RANDOMIZED CLINICAL TRIAL OF SINGLE VERSUS THREE DOSES OF CEFAZOLIN AS PROPHYLAXIS FOR NONPERFORATED ACUTE APPENDICITIS

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ABSTRACT

Background: The most common and significant cause for morbidity following emergency appendicectomy is surgical wound infection. There are conflicting reports regarding the optimal duration of antibiotic prophylaxis in nonperforated appendicitis. The efficacy of prolonged prophylactic antibiotic treatment in preventing wound infection for nonperforated appendicitis is poorly defined. **Objective:** A prospective randomized study was carried out to compare the efficacy of single dose cefazolin with three doses of cefazolin in reducing the incidence of postoperative wound infection for patients with nonperforated acute appendicitis.
Methods: One hundred patients with a clinical diagnosis of appendicitis were randomized into two groups. Group 1 received single intravenous dose of 1gm cefazolin at induction of anaesthesia and group 2 received two further doses of cefazolin following surgery. Postoperative wound infection was the primary endpoint. Results: The two groups were similar with regard to demographic data, pathologic condition of the appendix and duration of hospital stay. The postoperative wound infection rate was not significantly different among the two groups, 11% in group 1 and 9% group 2 (p =0.986). **Conclusions:** Single-dose cefazolin is equally effective to multiple-dose cefazolin in preventing postoperative wound infection in patients undergoing open appendicectomy for nonperforated acute appendicitis. However, because of the greater convenience and economic implications, single pre-operative dose of cefazolin is the choice of prophylaxis for nonperforated appendicitis.
Keywords: acute appendicitis, antibiotic, single dose, nonperforated

INTRODUCTION

Appendicectomy is one of the most common emergency surgical procedures with a postoperative wound infection rate of 1-10%[1-4]. Wound infection following open appendicectomy is a major cause for post-operative morbidity, prolonged hospitalization and increased costs. The pathologic state of the appendix is the most important determinant of postoperative wound infection following appendicectomy[5, 6]. The incidence of wound infection in patients with complicated appendicitis (perforated or gangrenous appendix) is nearly four to five times greater than that of nonperforated cases.

The efficacy of antibiotic prophylaxis in reducing wound infection in patients undergoing open appendicectomy is well established. Many randomized and observational studies have shown that appropriate use of antibiotics reduces the risk of infection by 40–60%[4, 7-10]. Based on prospective clinical studies, guidelines have been established regarding the choice of prophylactic antibiotics, it's timing and route of administration for emergency appendicetomy[11]. However, the

duration of antibiotic usage remains a contentious issue and there is no definite consensus among the surgical community[12, 13].

Single dose antibiotic prophylaxis has been recommended for majority of elective general surgical procedures[14]. In reality, this practice is not universally accepted and multiple dose regimens are still in use at many centres. In the emergency setting, though postoperative antibiotics are universally used for perforated appendicitis, no consensus exists regarding the efficacy of postoperative antibiotics in preventing surgical site infections in nonperforated cases. The main purpose of our study was to compare the efficacy of single dose of cefazolin with multiple doses of cefazolin in reducing the rate of wound infection in nonperforated appendicitis.

RESEARCH METHODOLOGY

A randomized prospective study of 100 patients with a clinical diagnosis of acute appendicitis presenting to the Emergency Department of Mahatma Gandhi Medical College was carried out over a period of two years. Before performing an emergency open appendicectomy, the patients were randomized into two groups by opening a sealed envelope containing details of the prophylactic antibiotic regimen to be used. Group 1 received single dose of cefazolin 1gm i.v. at time of induction of anaesthesia. In group 2, two further doses of cefazolin were given intravenously at 8 hours and 16 hours from the time of index surgery. Appendicectomy was carried out in all the patients by the standard protocol of open surgical technique. The surgical wound was closed in layers.

Exclusion criteria:

1.Gangrenous or perforated appendix
2. Abscess found at time of surgery
3. Allergic to cephalosporins
4. Prior antibiotic treatment

During the post-operative period, the progress of the surgical wound was monitored on a daily basis for all the patients included in the study. Wound infection was graded using the Southampton scoring system[15].

Southampton Scoring System

Grade	Appearance of wound
0	Normal healing
1	Normal healing with mild bruising
2	Erythema
3	Clear discharge
4	Purulent discharge
5	Deep wound infection

Wound healing was taken as normal for grades 0, 1 and 2. Infection of the wound was categorised as minimal for grade 3 and as major for grades 4 and 5. Patients who developed major infection were treated appropriately with daily wound irrigation and antibiotics based on culture reports.

Informed consent was obtained from all the patients and the study was carried out with prior clearance from the ethical committee.

Study parameters:

- Demographic data –age and sex
- Final histopathological report of the appendix
- Grade of wound infection
- Length of hospital stay

Statistical Method - Comparison of proportions by 'CHI Square' test.

RESULTS

In our study, 100 patients were included with a diagnosis of acute appendicitis and randomized to two groups, with fifty patients in each group. The age group varied from 15 to 55 years in both

groups, with a mean age of 28.2 years in group 1 and 29.1 years in group 2 (p=0.147) , as shown in table 1 and fig 1. The male to female ratio was 1.63 and 1.94 in group 1 and group 2 respectively (p=0.676) as shown in table 2 and fig 2.

The histopathological examination of the removed appendix revealed features of acute inflammation in 44(88%) patients in group 1 and 45(90%) in group 2. Six patients in group 1 and 5 from group 2 were excluded from the study in view of the presence of perforation, gangrenous or normal appendix (table 3 and fig 3).

In the postoperative period, the surgical wounds were examined and graded using the Southampton scoring system. Normal wound healing was observed in 34(77%) patients in group 1 and 37(82%) in the other group. Minimal wound infection which resolved spontaneously was present in 5 out of 44 patients (11%) in group 1 and 4 of 45 (9%) patients belonging to group 2. Discharge of pus (grade 4) was observed in 5(11%) patients in group 1 and 4(9%) in group 2. No patients in either group developed grade 5 wound infection.

Using Chi square test for analysis, the incidence pattern and the grade of wound infections in both the study groups were found statistically not significant(p=0.986), table 4 and fig 4.

The mean hospital stays of the single-dose and three-dose groups were 4.6 days and 5.2 days. The median duration of stay was 5 days in both groups. There was no significant difference in length of hospital stay between the two groups.

DISCUSSION

Usage of appropriate antibiotics is well known to control wound infection rates following open appendicectomy for uncomplicated acute appendicitis. While antibiotic prophylaxis is common in surgical procedures[16], inappropriate use of antibiotics occurs in 25–50% of general elective surgeries[17-21]. A Cochrane systematic review found that antibiotic use in patients having uncomplicated appendicitis was superior to placebo in reducing the rates of postoperative complications but concluded that no recommendations can be made regarding the duration of antibiotic use. At the same time, in patients with severe form of appendicitis, it has advised to continue a comprehensive antibiotic regime, as the risk of infective complications is quite high in this group[1].

The choice of antibiotic for prophylaxis varies widely in different centres and even among the different surgical units attached to the same Institute. The American Society of Health System Pharmacists (ASHP) recommends cephalosporins as drug of choice for prophylaxis for nonperforated appendicitis and gentamicin with metronidazole only in cases of penicillin allergy[22, 23]. The major controversy lies in the optimum duration of prophylaxis in cases of acute nonperforated appendicitis. Many studies have shown that single preoperative dose of antibiotic is as effective as multiple postoperative doses in preventing wound complications following appendicectomy[24-26].

A randomized control study by Mui et al have shown that single dose of preoperative antibiotic is adequate for prevention of infective complications of the wound in patients undergoing surgery for uncomplicated appendicitis. Their conclusion was that the prolonged antibiotic administration was cost-ineffective and led to unnecessary complications[27].

In our study, we have used a more objective method to assess the progress of the surgical wounds by correlating with the Southampton scoring system. There was no significant difference (p=0.986) between wound infection rates of the single-dose group (11%) and the three-dose group (9%). These findings are in full agreement to the similar studies in the literature[24-27]. Moreover, comparing the incidence of wound infection across all the grades in both the groups by using the Chi-square test has shown no significant difference between the two groups(p=0.986). Cefazolin was chosen in our

study as it was readily available, cheaper and has very good antibacterial spectrum for pathogens causing post appendicectomy sepsis. This choice of antibiotic is in line with the recommendations given by the ASHP[22]. We also found from our study that there was no significant difference in the length of the hospital stay between the two groups. The median duration of stay in both groups was 5 days.

Many studies have highlighted and repeatedly emphasised the effects of improper choice and inappropriately prolonged duration of prophylactic antibiotics on the rising emergence of antimicrobial resistance among the common pathogens[28-33]. Coakley et al, in a recent study, have consistently proven that postoperative antibiotic treatment for nonperforated appendicitis did not reduce infectious complications. In fact, their study showed significantly increased rate of adverse effects like Clostridium difficile infection, diarrhea, longer length of hospital stay and higher treatment cost. Patients receiving postoperative antibiotics were also more frequently readmitted and reoperated[34].

A possible benefit that can be derived from our study is that by using a single preoperative dose, the surgeon can be certain of having given an effective prophylaxis at induction of anaesthesia without the need to monitor further postoperative doses. Moreover, avoiding further intravenous doses of antibiotics may lead to savings in terms of nursing effort, time and the cost of treatment.

CONCLUSION

It is evident that prophylactic postoperative doses of cefazolin confer no additional benefit over a single preoperative dose of cefazolin. With additional benefits of the greater ease of administration and decreased cost, single-dose cefazolin is the prophylaxis of choice for appendicectomy in patients with nonperforated appendicitis. It is essential for surgeons and surgical departments to update their routine practice of antibiotic prophylaxis to comply with updated guidelines and evidence base.

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Table 1: Demographic data of the study groups

Age in years	Group 1 (single dose)		Group 2 (multiple dose)	
	Male	**Female**	**Male**	**Female**
15-25	15	10	19	9
26-35	10	6	10	7
36-45	4	3	1	0
46-55	2	0	3	1
Total	31	19	33	17

Samples are age matched with p=0.147

Figure 1: Age distribution

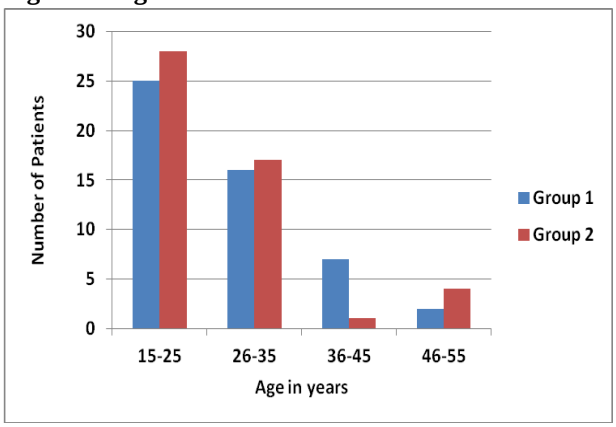

Figure 3: Pathology of the appendix

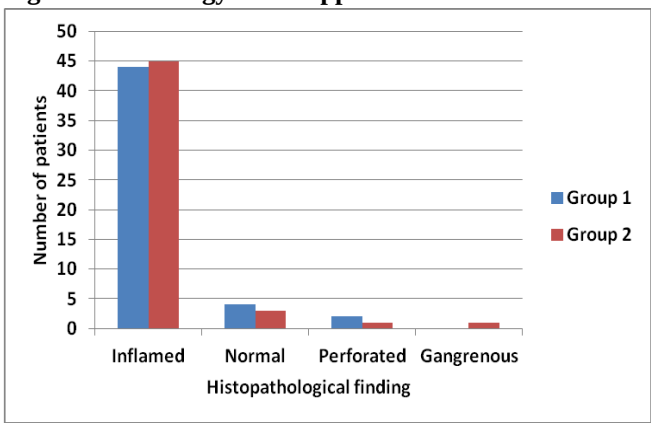

Table 2:Male - female ratio

Gender of the patients	Group 1		Group 2	
	No.	%	No.	%
Male	31	62	33	66
Female	19	38	17	34
Total	50	100	50	100

Samples are gender matched, p= 0.676

Figure 2: Sex ratio in the study groups

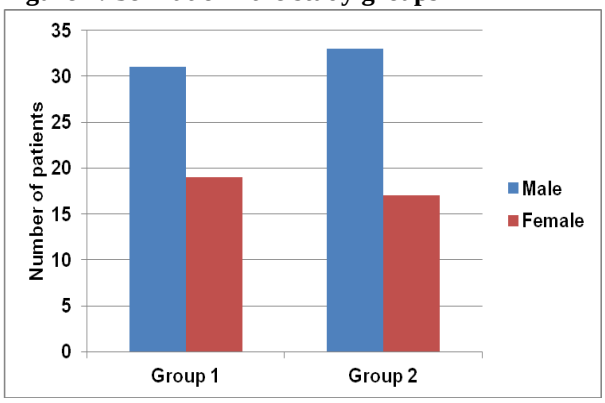

Table 3: Histopathological report of appendix

Report	Group 1	Group 2
Inflamed	44(88%)	45(90%)
Normal	4(8%)	3(6%)
Perforated	2(4%)	1(2%)
Gangrenous	0	1(2%)
Total(n=100)	50	50

Pathologic status of appendix were similar in both groups, p=0.685

Table 4: Grade of wound infection – Southampton scoring system

Grade	Group 1(n=44)	Group 2(n=45)
0	18(41%)	19(43%)
1	9(21%)	10(22%)
2	7(16%)	8(17%)
3	5(11%)	4(9%)
4	5(11%)	4(9%)

Wound infection rates across all grades were similar in both groups, p =0.986

Figure 4: Grade of wound infection