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THE EFFECT OF EMPIRICAL VS CULTURE-BASED THERAPY ON PATIENT OUTCOMES WITH COMPLICATED INTRA-ABDOMINAL INFECTION AT KHYBER TEACHING HOSPITAL PESHAWAR

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Abstract
Intra-abdominal infections are peritoneal inflammation in response to microorganisms, resulting in pus formation in the peritoneal cavity. Intra-abdominal infections are of two types: uncomplicated and complicated based on the severity of the infection. To compare the efficacy of empirical and culture-based therapy in a patient with complicated intra-abdominal infections presenting to Khyber Teaching Hospital Peshawar, a total of 694 patients of both genders with complicated intra-abdominal infections were included in the study. A sample size of 347 patients was calculated for the culture-based therapy group or Group A while 347 sample size for the empirical therapy group or Group B. Efficacy was noted after the 14th day for both groups. The age range in this study was 15 to 65 years with a mean age of 31.204±10.96 years, a mean duration of disease 55.659±18.27 hours, and a mean weight of 71.400±11.72 Kg in Group A. The mean age of the patients in Group B was 29.953±9.79 years, the mean duration of disease was 56.005 ± 18.19 hours and the mean weight was 70.308±10.81 Kg in Group B. Efficacy was observed in 310 (89.3%) patients in group A as compared to 296 (85.3%) patients in group B (P= 0.110). Our study showed that Moxifloxacin monotherapy was as well tolerated and effective as culture-based therapy in the treatment of patients with complicated intra-abdominal infections

Keywords: Intra-abdominal infections, Empirical therapy, Culture-based therapy, Efficacy

1. Introduction

Intra-abdominal infections are defined as peritoneal inflammation in response to microorganisms, resulting in purulence in the peritoneal cavity. Intra-abdominal infection is classified as either uncomplicated or complicated based on the severity of the infection.[1-3] Uncomplicated intra-abdominal infection involves a single intra-abdominal organ without anatomical disruption.[4-6] Complicated intra-abdominal infection extends beyond the organ that is the source of infection, and causes either localized peritonitis, referred to as an abdominal abscess, or diffuse peritonitis.[7, 8] Intra-abdominal infections constitute the primary diagnosis in 8% of hospitalizations, and they are the second most common infectious aetiology associated with mortality in intensive care units.[9] The overall mortality is 9.2% to 10.5%. [10-12]The mean age is 62 years and the majority of the patients are male.[13] The major pathogens involved in intra-abdominal infections are Enterobacteriaceae.[14] Complicated intra-abdominal infections are common surgical emergencies so proper effective

treatment is necessary with early recognition, fluid resuscitation, effective antimicrobials, and adequate source control[15, 16].

Complicated intra-abdominal infections are divided into three major categories i-e, 1) peritoneal and intra-peritoneal infections that involve the abdomen, bowels, and peritoneum, 2) intra-biliary infections, cholecystitis, and cholangitis, and 3) pancreatitis. [17]Early clinical diagnosis and prompt treatment in critically ill patients are the cornerstones in the management of complicated intra-abdominal Infections.[18] The management of complicated intra-abdominal infections involves an operative or percutaneous intervention to obtain surgical control of the source. Empiric antimicrobial therapy with appropriate agents is an important component of the treatment. [19-21]
A study by de Ruiter J *et al.* has shown that the efficacy of culture-based therapy was 87% in complicated intra-abdominal infections.[16] Another study by Malangoni MA, et al have shown that the efficacy of empirical therapy was 80% in complicated intra-abdominal infections.[22]
Billing *et al.* demonstrated the reliability of MPI in 2003 patients from 7 centers in Europe. With a threshold index score of 26, the sensitivity was 86 (range 54-98) percent, specificity 74 (range 58-97) percent, and accuracy 83 (range 70-94) percent in predicting death. [23]For patients with a score, less than 21 the mean mortality rate was 2.3 (range 0-11) percent, for scores 21-29 22.5 (range 10.6-50) percent, and scores greater than 29 59.1 (range 41-87) percent[5].

For adequate antimicrobial therapy, intra-abdominal culture may be helpful and may reduce the use of broad-spectrum antimicrobials.[24] Despite official guidelines, there is a lack of evidence from the controlled trials about empiric coverage for Enterococcus, anaerobes, and multiple drug-resistant organisms. Recent guidelines recommend obtaining cultures from peritoneal fluid in high-risk patients, but these recommendations are mostly based on studies of patients with perforated appendicitis.[22, 25, 26] as sufficient studies based on abdominal culture are not available neither internationally nor locally in complicated intra-abdominal infections, this study is planned to compare the efficacy of empirical and culture-based therapy in a patient with complicated intra-abdominal infections.[27-29] The results of this study will help practitioners to select better modalities for the treatment of complicated intra-abdominal infections. The objective of this study was to compare the efficacy of empirical and culture-based therapy in a patient with complicated intra-abdominal infections presenting to Khyber teaching hospital Peshawar.

2. Methodology

Complicated Intraabdominal Infection: It was defined as a patient presenting with fever >37.5°C [>99.5°F] oral/tympanic and abdominal pain (VAS> 4) and tense tender abdomen (on physical examination) with perforation of the gastrointestinal tract (damage to all the layers of the intestine causing spillage of fecal matter leading towards peritonitis and diagnosed by absent bowel sounds) on ultrasound. For efficacy; it was defined as complete resolution of infection without the need for surgical intervention and no symptoms of infection. Whereas, the proposed hypothesis was that there is a difference in efficacy of empirical versus culture-based therapy in a patient with complicated intra-abdominal infections presenting to Khyber teaching hospital Peshawar.

3. Materials and statistical model

The study design selected was a Randomized Controlled Trial, which was set at the surgical department of Khyber Teaching Hospital Peshawar from 10th October 2020 to 30th April 2021. For the proposed study non-probability consecutive sampling was used with a sample size of 694 (347 in each group), whereas, the sample size was calculated using WHO software. With the hypothesis test, two proportions (one-sided) is used with an assumption of having a Significant level= 5%, statistical power= 80%, anticipated proportion I= 87% and Anticipated proportion II= 80%.
The sample selection includes 15-65 years old patients of either gender, complicated intra-abdominal infections as per operational definition, duration of complaints >24 hours, patients who underwent

elective or emergency exploration, ASA grade I & II patients from the Surgical Department of Khyber Teaching Hospital Peshawar were included in the study after permission from the ethical committee. Randomization was done by blocked randomization. 347 sample sizes for the culture-based therapy group or Group A while 347 sample sizes for empirical therapy group or Group B.

In group A, samples of abdominal fluid were taken during the first procedure. All specimens were cultured for the identification of microorganisms. Antibiotics were given as per microorganism sensitivity as per our department protocol for 14 days. In group B, empirical therapy of sequential (IV/PO) moxifloxacin, 400 mg IV every 24 hours, followed by moxifloxacin, 400 mg PO every 24 hours was given for 14 days.

Efficacy was noted after the 14^{th} day as per operational definition from both groups and recorded on specially designed proforma. Data were analysed with a statistical analysis program (SPSS version 22). Analysis was done to compare the proportion of group A and group B. Frequencies and percentages were computed for qualitative variables like gender, ASA grade, type of exploration, and efficacy. Mean ±SD was presented for quantitative variables like age, duration of complaint, and weight (on the weighing machine). A Chi-square test was applied to compare efficacy in both groups taking $p \leq 0.05$ as significant. Stratification was done with regard to age, gender, duration of complaint, ASA grade, and type of exploration to see the effect of these variables on efficacy. Post-stratification analysis was done using the chi-square test for both groups and a p-value of ≤ 0.05 was considered statistically significant**.**

4. Result and discussion

The age range in this study was 15 to 65 years with a mean age in this study was 31.204±10.96 years, a mean duration of disease of 55.659±18.27 hours, and mean weight was 71.400±11.72 Kg in Group A, and mean age of 29.953±9.79 years, mean duration of disease 56.005±18.19 hours and mean weight was 70.308±10.81 Kg in Group B as shown in Table-I.

Table- I: Means of patients according to age, duration of disease and weight (n=694)

Demographics	**Group A (n=347, Mean±SD)**	**GroupB (n=347,Mean±SD)**
Age (years)	31.204±10.96	29.953±9.79
Duration of disease (hours)	55.659±18.27	56.005±18.19
Weight (Kg)	71.400±11.72	70.308±10.81

Male gender was dominant in both groups as shown in Table S-I. The frequency and percentage of ASA grade and type of exploration in both groups are shown in Table S-II and S-III respectively. Efficacy was observed in 310 (89.3%) patients in group A as compared to 296 (85.3%) patients in group B (P= 0.110) as shown in Table S-V. Stratification of efficacy in both groups with regard to age, gender, duration of complain, ASA grade, type of exploration are shown in Table-II, S-IV, S-V, S-VI (Supplementary data) and III respectively.

Table- II: Stratification of efficacy with respect to age in both groups
For Age group 15-40 years

Group	**Efficacy**		**P value**
	Yes	**No**	
A	255(89.5%)	30(10.5%)	**0.275**
B	257(86.5%)	40(13.5%)	

For the Age group 41-65 years

Group	Efficacy		P value
	Yes	No	
A	55(88.7%)	7(11.3%)	0.125
B	39(78%)	11(22%)	

According to the guidelines, for complicated intra-abdominal infections, single agents such as ampicillin-sulbactam, ertapenem as well as cefazolin or a combination of cephalosporins, levofloxacin or ciprofloxacin and metronidazole are recommended. Potential treatments for more severe community-acquired infections include regimens such as imipenem–cilastatin, piperacillin-tazobactam, and meropenem as well as third- or fourth-generation cephalosporins plus metronidazole. In this trial, monotherapy with moxifloxacin was as effective as a culture-based therapy for mild-to-moderate and more severe complicated intra-abdominal infections. Efficacy was observed in 310 (89.3%) patients in group A as compared to 296 (85.3%) patients in group B (P= 0.110). A study by de Ruiter J. et al. have shown that the efficacy of culture-based therapy was 87% in complicated intra-abdominal infections. Another study by Malangoni MA, et al has shown that the efficacy of empirical therapy was 80% in complicated intra-abdominal infections[19, 30].

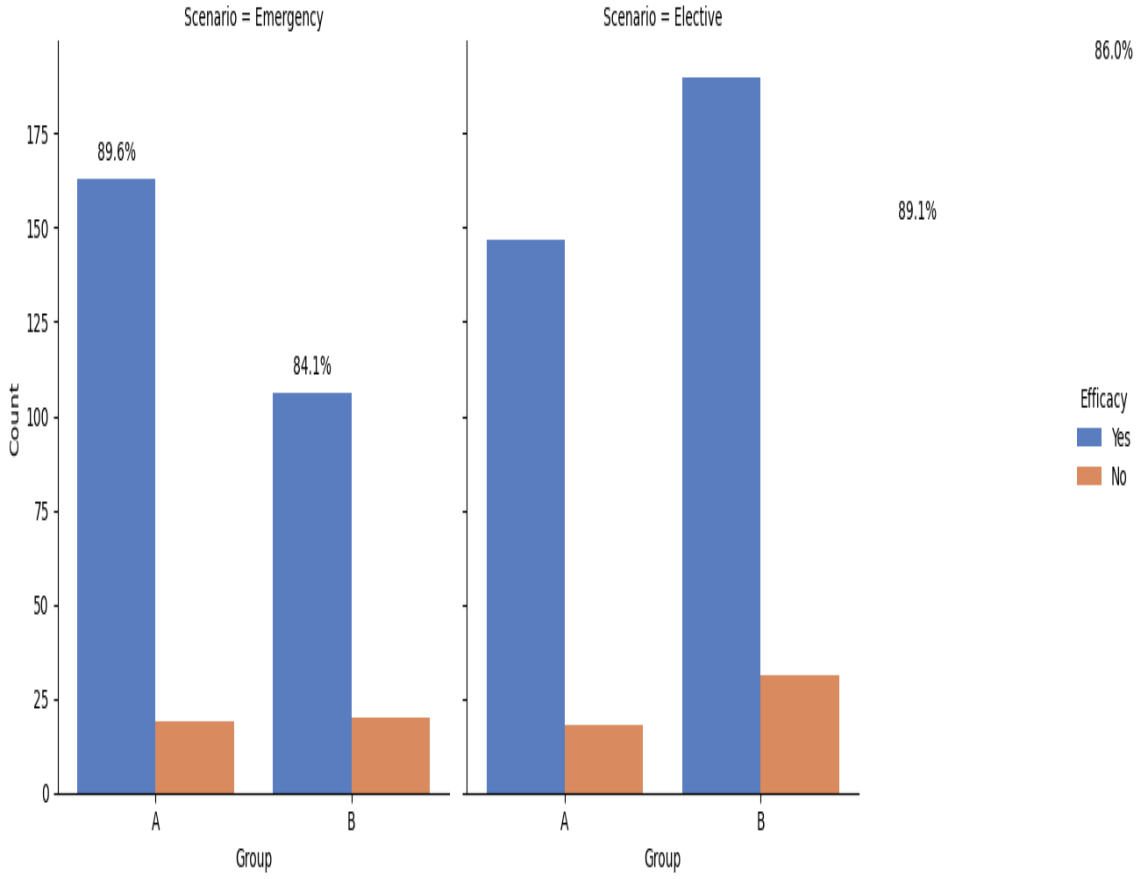

Table- III: Stratification of efficacy with respect to type of exploration in both groups

For emergency

Group	Efficacy		P value
	Yes	No	
A	163(89.6%)	19(10.4%)	0.159
B	106(84.1%)	20(15.9%)	

For elective

Group	Efficacy		P value
	Yes	No	
A	147(89.1%)	18(10.9%)	**0.363**
B	190(86%)	31(14%)	

More resistant bacteria often cause hospital-acquired intra-abdominal infections, therefore, treatment may require combination regimens based on local susceptibility patterns. In this study, the organisms causing the hospital-acquired infections tended to have higher MIC90 values for moxifloxacin (as well as for culture-based therapy) than the community-acquired organisms. Despite this, moxifloxacin provided a higher clinical cure rate and bacteriologic cure rate when compared to other regimens for hospital-acquired infections. In addition, moxifloxacin was effective for both mild-to-moderate and more severe hospital-acquired infections providing clinical cure rates[31].

A previous report has demonstrated more favourable outcomes for patients with complicated intra-abdominal infections enrolled in prospective randomised clinical trials. Patients not entered in these studies tend to be older and have higher APACHE II scores than patients in clinical trials. Newer agents also have a lower incidence of antimicrobial resistance, which is associated with a decreased incidence of treatment failure. This may account in part for the better clinical cure rate with moxifloxacin treatment in the present study.

One recent surveillance study demonstrated a higher prevalence of fluoroquinolone-resistant Bacteroides spp. than previously reported[32]. However, this report included only isolates from 12 large tertiary care medical centers, and such studies may not reflect susceptibility rates among community-acquired pathogens. Clinical cure rates for patients infected with B. fragilis or B. thetaiotaomicron were at least as good for moxifloxacin as for the comparator regimen. Also, although the moxifloxacin MIC90 values (but not the values for culture-based therapy) were higher for B. fragilis and B. thetaiotaomicron among patients who failed therapy, there was no correlation between individual MIC values and clinical or bacteriologic success or failure. However, this may reflect the relatively small number of patients infected with one of these organisms who subsequently failed moxifloxacin therapy [33].

Although comparisons between studies must be made with caution, moxifloxacin efficacy rates in the current study are consistent with those obtained with other recommended treatment regimens, including ciprofloxacin plus metronidazole, piperacillin-tazobactam, and imipenem-–cilastatin [25]. Further studies need to be conducted that directly compare fluoroquinolones with or without metronidazole in complicated intra-abdominal infections. In addition, local susceptibility patterns to Bacteroides spp. should also be considered when choosing monotherapy or combination therapy.

5. Conclusion

Our study showed that Moxifloxacin monotherapy was as well tolerated and effective as culture-based therapy in treating patients with complicated intra-abdominal infections. Moxifloxacin, which can be given once daily, can be considered a useful and convenient option for this treatment.

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Supplementary Data

Table-I: Frequency and percentage of gender in both groups

Gender	Group A (n=347)	Group B (n=347)
Male	264(76.1%)	182 (52.9%)
Female	83 (23.9%)	165 (47.6%)
Total	347 (100%)	347 (100%)

Table-II: Frequency and percentage of ASA grade in both groups

ASA grade	**n=347**	**n=347**
	Group A	**Group B**
I	280(80.7%)	307(88.5%)
II	67 (19.3%)	40 (11.5%)
Total	347 (100%)	347 (100%)

Table-III: Frequency and percentage of type of exploration in both groups

Type of exploration	**n=347**	**n=347**
	Group A	**Group B**
Emergency	182(52.4%)	126(36.3%)
Elective	165 (47.6%)	221 (63.7%)
Total	347 (100%)	347 (100%)

Table-IV: Comparison of efficacy in both groups

Efficacy	n=347	n=347	P Value
	Group A	Group B	
Yes	310 (89.3%)	296 (85.3%)	0.110
No	37 (10.7%)	51 (14.7%)	
Total	347 (100%)	347 (100%)	

Table- V: Stratification of efficacy with respect to gender in both groups

For male gender

Group	Efficacy		P value
	Yes	No	
A	235(89%)	29(11%)	0.127
B	153(84.1%)	29(15.9%)	

For female gender

Group	Efficacy		P value
	Yes	No	
A	75(90.4%)	8(9.6%)	0.400
B	143(86.7%)	22(13.3%)	

Table- VI: Stratification of efficacy with respect to duration of disease in both groups For 24-48 hours

Group	Efficacy		P value
	Yes	No	
A	225(88.9%)	28(11.1%)	0.107
B	216(84%)	41(16%)	

For > 48 hours

Group	Efficacy		P value
	Yes	No	
A	85(90.4%)	9(9.6%)	0.732
B	80(88.9%)	10(11.1%)	

Table- VIII: Stratification of efficacy with respect to ASA grade in both groups

For ASA I

Group	Efficacy		P value
	Yes	No	
A	247(88.2%)	33(11.8%)	0.567
B	266(86.6%)	41(13.4%)	

For ASA II

Group	Efficacy		P value
	Yes	No	
A	63(94%)	4(6%)	0.005
B	30(75%)	10(25%)	