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Comparison of antibiotic usage, third generation cephalosporin single dose vs multiple dose in cases of interval open appendicectomy.

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Abstract

Background: Single or multiple dosages of antibiotics play an important role to prevent surgical site infections. The main goal of prophylaxis antibiotic usage is to ensure effective serum and tissue levels of the drug for the entire duration of surgery.

Methods: A total of 76 patients who underwent Interval open Appendicectomy under spinal anaesthesia were included in the study for a period of 2 years, from September 2019 to October 2021. Simple Rando misation of the patients into two groups were done using computer derived software. Group A: Received single dose of ceftriaxone sulbactam 1.5gm i. v. at time of induction of anaesthesia. In group B: two further doses of Ceftiaxone sulbactam was given intravenously 12th hourly for 3 days

Results: In this study, 18 female patients (47.4%) in single dose regimen is lower than in the multiple dose regimen 21 female patients (55.3%) and 20 males (52.6%) in single dose is higher than the multiple dose regimen 17 males (44.7%). The mean age of multiple dosage group was 37.63 with SD of 10.51 which was slightly higher than single dosage group that is 36.53 with SD of 10.49. Majority of the patients in Single dose group had a duration of hospital stay of 5 days and

majority of the patients in Multiple dose group had a duration of hospital stay of either 4 days or 5 days.

Conclusion: Single dose of pre operative antibiotic (Ceftriaxone plus Sulbactum) would be sufficient in cases of interval appendicectomy for simple uncomplicated nonperforated appendicitis in controlling SSIs. Postoperative anti biotics did not add an appreciable clinical benefit in these patients

Keywords: Open interval Appendicectomy, Third generation Cephalosporin, Single dosage, Multiple dosages.

Introduction

The most common emergency surgical condition is acute appendicictis.[1] It is the most frequent cause of acute abdominal pain with a lifetime risk of 7%.[2] Emergency appendicectomy is the usual treatment modality with more than 300,000 performed annually in the United States.[3] Peak age is 15-25 years with higher risk in males.[4] Surgical site infection (SSI) is the most common post-op complication despite improved peri-operative care and antibiotics and in uncomplicated appendicitis, it is less than 10%.[5,6] Non perforated appendicitis is considered as clean wound whereas contaminated and perforated appendicitis as contaminated wound. It is shown that pre-operative antibiotic is effective in reducing SSIs.[7,8] In perforated cases post operative antibiotic usage seems logical and necessary whereas in non-perforated cases their usage does not seem logical.[7,9,10] Patients undergoing clean surgery (eg. Breast, Hernia) around 1% of them and patient undergoing clean contaminated surgery (e.g., colorectal) 11% of them experience surgical site infections.[11]

Most common nosocomial infections in surgical patients are Surgical site infections and accounting approximately 500,000 infections annually in USA alone.[12] Nearly 4 million excess hospital days annually and nearly 2 billion US dollar in increased health care costs in the United States is caused by Surgical site infections. Those patients who develop SSI are five times more likely to be readmitted to hospital, 60% more likely to stay in Intensive care unit (ICU) and twice likely to die compared to normal surgical patients without infections.

In different surgical procedures the role of prophylactic antibiotic is well established but the drug of choice and its dosage is still a matter of debate.[13,14]

Prophylactic antibiotic therapy should be directed against the bacteria which most commonly contaminate the wound.

The main goal of prophylaxis antibiotic usage is to ensure effective serum and tissue levels of the drug for the entire duration of surgery. Single or multiple dosages of antibiotics play an important role to prevent Surgical site infections. Generally, a single prophylaxis dose of antibiotic is given 30-60 minutes preoperatively.[15] If surgery is ≥ four hours or twice the half-life of the antibiotic used, a second dose is administered.

The aim of this study was to know the outcome of single dose antibiotic in cases of interval open appendicectomy and to compare single dose with multiple doses of antibiotics in cases of interval open appendicectomy by analysing the rate of occurrence of post-operative infections: systemic, abdominal and surgical site infections in 2 Randomised groups and to compare the total duration of hospital stay in both the groups.

Materials and methods

The study is a hospital based Randomised Controlled Trial, Double Blinded study in the Department of Surgery, Regional Institute of Medical Sciences (RIMS), Imphal, for a period of 2 years from September 2019 to October 2021**.** Simple Randomization of the patients into 2 groups was done using a computer derived software.

Group A

Received single dose of ceftriaxone sulbactam 1.5gm intravenously at the time of induction of anaesthesia. In group B: Two further doses of Ceftriaxone sulbactam was given intravenously 12th hourly for 3 days.

Appendicectomy was carried out in all the patients by the standard protocol of open surgical technique. The surgical wound was closed in layers. During the post-operative period, the progress of the surgical wound was monitored on a daily basis for any signs of fever, discharge from wound site, localised swelling, redness heat, stitch abscess, wound gap, abdominal distension.

Sample size calculation formula:

$n = [(u+v)^2 * (S_1^2 + S_2^2)] / (m_1 - m_2)^2$

Power 80% = 0.84

u= one sided % point of normal distribution corresponding to 100% - 80% = 0.84

95% degree of precision (or 5% level of significance)

v= Two sided % of normal distribution corresponding to 5% level of significance= 1.96

S1= standard deviation before study

S2= Standard deviation after study

m1= mean before study

m2= mean after study

Sample size taking 10% non-response rate was 38 in each group.

Total sample size in this study 38 + 38 = 76

Wound infection was graded using the Southampton scoring system.[16]

Southampton scoring system

grade	appearance of wound
0	Normal healing
1	Normal healing with mild bruising
2	Erythema
3	Clear discharge
4	Purulent discharges
5	Deep wound infection

Wound healing was taken as normal for grades 0, 1 and 2. Infection of the wound was categorized minimal for grade 3 and as major for grades 4 and 5.

Patients who had major infection were treated appropriately with daily wound irrigation and antibiotics based on culture reports. Patients were called for follow up examination after discharge on 7th and 21st postoperative days. The type of antibiotic usage and duration of hospital stay were noted in both groups.

Statistical Analysis:

Collected data were tabulated and analyzed accordingly using SPSS Software 26 Version (IBM Corp., Armonk, NY, United States). Chi-Square Test and Students' t Test as appropriate were used. P value < 0.05 was considered as statistically significant.

Ethical issues

Ethical Approval were obtained from the Institutional Research Ethics Board (REB), Regional Institute of Medical Sciences, Imphal before commencement of the study. REB reference no. is: A/206/REB-Comm (SP)/RIMS/2015/616/94/2019. Trial was prospectively registered in Clinical Trial Registry of India (CTRI). CTRI no. is CTRI/2021/02/030909 received on 1st February, 2021.

Results

The percentage of females (47%) in single dose regimen is lower than in the multiple dose regimen (55%) and percentage of males (53%) in single dose is higher than the multiple dose regimen (45%). Out of 76 patients, 44 had comorbidities. More participants (60.5%) had comorbidities in single dose group**.** Diabetes and Hypertension were more in Single dose group whereas patients with Asthma were more in Multiple dose group. Majority of the patients in Single dose group had a duration of hospital stay of 5 days and majority of the

patients in Multiple dose group had a duration of hospital stay of either 4 days or 5 days.

Background characteristics	Total n (%)	Single dose n (%)	Multiple dose n (%)	P value
Age (mean±SD)	76 (100)	36.53±10.49	37.63±10.53	0.648*
Gender				
Female	39 (51.3)	18 (47.4)	21(55.3%)	0.491**
Male	37 (48.7)	20(52.6%)	17(44.7%)	
Comorbidity				
Present	44(57.9%)	23(60.5%)	21(55.3%)	0.642**
Absent	32(42.1%)	15(39.5%)	17(44.7%)	
Duration of hospital stay (mean±SD)	76	4.66±0.82	4.42±0.89	0.230*

Independent sample t test **Chi-square test

Table 1: Comparison of both groups in terms of background characteristics (N=76)

Application of independent sample t test, it was seen both groups were comparable in term of age (p= 0.648). Similarly on application of Chi-square test it was seen both the groups were not significantly different in term of gender (p = 0.491) and comorbidity (p = 0.642). Duration of hospital stay was not significantly different between the two groups (p>0.05).

Complications	**Single Dose (N=38)**		**Multiple Dose (N=38)**		**P Value**
	Absent n (%)	**Present n (%)**	**Absent n (%)**	**Present n (%)**	
Pyrexia	33(86.84)	5(13.16)	31(81.57)	7(18.53)	0.53*
Localised Pain	33(86.84)	5(13.16)	35(92.10)	3(7.9)	0.46**
Discharge from wound	32(84.21)	6(15.79)	30(78.94)	8(21.06)	0.55*
Localised swelling	33(86.84)	5(13.16)	34(89.47)	4(10.53)	0.72**
Localised Redness	32(84.21)	6(15.79)	29(76.31)	9(23.69)	0.39*
Stitch abscess	32(84.21)	6(15.79)	35(92.10)	3(7.9)	0.29**
Abdominal distension	35(92.10)	3(7.9)	32(84.21)	6(15.79)	0.29**
Wound gap	34(89.47)	4(10.53)	31(81.57)	7(18.53)	0.33*
Secondary suturing	31(81.57)	7(18.43)	33(86.84)	5(13.16)	0.53*

*Chi square test **Fisher's exact test

Table 2: Comparison of post-operative complication occurrence on day 7 between the two groups (N=76)

On 7th post operative day, complication of pyrexia was similar in both group (p=0.53), similarly localised pain (p=0.46), discharge from wound (p= 0.55), localised swelling (p=0.72), localised redness (p=0.39), stitch abscess (p=0.29), abdominal distension (p=0.29), wound gap (p=0.33) and secondary suturing (p=0.53) were not significantly different in both the group.

Complication	Single Dose		Multiple Dose		P Value
	Absent	Present	Absent	Present	

Pyrexia	31	7	32	6	0.76*
Localised Pain	31	7	34	4	0.33*
Discharge from wound	30	8	29	9	0.78*
Localised swelling	33	5	33	5	1.0*
Localised Redness	32	6	28	10	0.26*
Stitch abscess	33	5	36	2	0.23**
Abdominal distension	35	3	32	6	0.29**
Wound gap	33	5	32	6	0.74*
Secondary suturing	30	8	33	5	0.36*

* Chi square test ** Fisher's exact test

Table 3: Occurrence of Post-operative infectious complication on day 21.

By the 21st post operative day, complication of pyrexia was similar in both group (p = 0.76), similarly localised pain (p = 0.33), discharge from wound (p = 0.78), localised swelling (p=1.0), localised redness (p= 0.26), stitch abscess (p=0.23), abdominal distension (p= 0.29), wound gap (p= 0.74) and secondary suturing (p= 0.36) were not significantly different in both the group.

Discussion

Single or multiple doses of prophylactic antibiotics are important to prevent SSIs. In addition to this, pre-operative preparation of the patient, intra operative aseptic techniques and precautions and meticulous surgery are also equally important to prevent post operative wound infection. A single, effective, nontoxic drug is used to prevent infection by a specific microorganism or to eradicate an early infection.

Despite improved surgical techniques, post-operative complications including wound infection and intra-abdominal abscess still account for a significant rate of morbidity. It has been shown that prophylactic antibiotic is effective in prevention of post operative complications in appendicectomies patients, whether the administration is given pre-, peri or post operatively. There is variation in the incidence of post operative infection for non-perforated appendicitis ranging from 0 to 11.7%. These discrepancies could be attributed to the differences in the number of the patients, type of antibiotic used, follow-up duration and definition of wound infection.

Our study comprised of 76 patients in whom the age varied from 21 years to 58 years. The overall mean age of the patients with appendicitis in this study was 37.08 years with a standard deviation of 10.5 years. This is higher than the mean age recorded by Ahmed BS et al[17] recorded a mean age of 26.35 years. Xu S et al[18] recorded a mean age of 40.3 years with a standard deviation of 17.3 years and age varied from 19 to 88 years. Sadraei Moosavi SM et al[19] recorded a mean age of 28.37 years with a standard deviation of 10.88 years.

The mean age of the patient in the single dose regimen was 36.53 years with a standard deviation of 10.49 years and the mean age of multiple dose regimen was 37.63 years with a standard deviation of 10.51 years. Thus, age of the patients in the present study was almost alike. This neutralized any influence of age of patient may have on the main finding of the study. Bangaru H et al[16] recorded a mean age of 23.57 years with a standard deviation of 4.18 years in single dose regimen and 22.96 years with standard deviation of 3.41 years in multiple dose regimen. Sadraei Moosavi SM et al[18] recorded a mean age of 28.45 years with a standard deviation of 11.06

years in single dose regimen and 28.30 years with standard deviation of 10.70 years in multiple dose regimen. There was no statistically significant difference between mean age in the two groups.

The total number of female patients in the present study was 39 (single dose = 18, multiple dose = 21) 51.3% and male patients were 37 in number (single dose = 20, multiple dose = 17) 48.7% among them in single dose group male patients were more in number (52%) and in multiple dose group female patients were more in number (55.3%) which was not statistically significant with p value of 0.491. This is comparable with the study conducted by Coakley BA et al[20] where male patients were more in number (52.03%) in single dose group and female patients were more in number (58.3%) which was not statistically significant. Bangaru H et al[16] conducted a study where both in single dose group and in multiple dose regimen males were more in number 55.0% and 57.3% respectively. These differences were because of different study population and different study setup.

In our study, we found that post operative complications in the both the age group on Day 7 in terms of Pyrexia, Localised pain, Discharge from wound, Localised swelling, Localised redness, Stitch abscess, Abdominal distension, Wound gap, Secondary suturing were not significant with p values of 0.53, 0.46, .55, 0.72, 0.39, 0.29. 0.29, 0.33, 0.53 respectively and on Day 21 p values were 0.76, 0.33, 0.78, 1.0, 0.26, 0.23, 0.29, 0.74, 0.36 respectively. There was no statistically significant difference in the rate of surgical site infection in Group A and Group B. This is comparable with the study conducted by Bangaru H et al[16] where the rate of surgical site infection in Group A was 2.5% and in Group B was 3.6% and the difference was not statistically significant (p= 0.6705; Chi square test). Similar findings were observed in the study of Ahmed BS et al[16] where the rate of post operative complications in Group A was 5.2% and in Group B was 5.3% and it was not statistically significant with p value of 0.4713. Sadraei-Moosavi SM et al[18] found no statistical difference in the rates of surgical site infections in both the groups. Xu Set al[17] in their study found no statistical difference between the antibiotic selection and SSIs with p value of 0.8755 and 0.9184 in Mono-variate and Multivariate analysis in both the Group. In a study by Coakley BA et al [19] it was found that postoperative antibiotics did not alter the incidence of superficial SSIs, deep SSIs, or organ space SSIs (all p = 0.1), but did correlate with higher rates of Clostridium difficile infection (p = 0.02), urinary tract infection (p = 0.05), postoperative diarrhoea (p < 0.001).

Strength of the study: One of the major strengths is that our study employed a representative sample of the population and hence the study results could be generalised to similar setting. Moreover, our study is the first Randomised Controlled Trial conducted in Manipur where post operative complications were compared between single and multiple doses groups that makes the study unique.

Limitation of the study: The intervention of the study could not be conducted according to the predetermined timeframe due to COVID-19 pandemic. This also affected the admission rate of the patients of appendicitis in the hospital making it difficult to reach the sample size. Small sample size of the study could be another limitation. Thus, further large-scale studies involving more patients across different centres is needed.

Conclusion

The detailed comparison of the efficacy of the prophylactic antibiotics in the single dose and multiple dose regimen concluded that single dose of pre-operative antibiotic (Ceftriaxone plus Sulbactum) would be sufficient in cases of interval appendicectomy for simple

uncomplicated nonperforated appendicitis in controlling SSIs. Postoperative antibiotics did not add an appreciable clinical benefit in these patients. As a consequence, surgeons need to update their practice of the antibiotic prophylaxis according to standard guidelines and evidence-based medicine.

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