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PATTERNS OF PRESCRIPTION AND USAGE OF ANTIMICROBIAL AGENTS FOR THE PROPHYLAXIS OF SURGICAL SITE INFECTIONS IN A TERTIARY CARE HOSPITAL IN KARNATAKA, SOUTH INDIA

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ABSTRACT

Background: Surgical Site Infections (SSI) are considered to be the most common post-operative complication and second most common cause of nosocomial infections. The administration of empirical antimicrobials preoperatively is one of the measures used to overcome risk of developing SSI .There is a need to generate basic database on the current prescription pattern of prophylactic antimicrobials in institutions all over India so that it can be used for understanding the ongoing trend before any organization can put forward recommendations or provide national guidelines. **Aim:** This study aims to explore the current prophylactic antimicrobials prescription pattern followed in surgical department in a tertiary care hospital in Karnataka, South India. **Methodology:** A prospective study was carried out in Surgery department of a tertiary care hospital for a period of 12 months. Inpatients undergoing surgical procedures in Surgery department were included and data collected on baseline characteristics, surgical procedure, choice of prophylactic antibiotic, timing of administration, duration and dosage. Each patient was followed up till discharge from hospital. Institutional ethical clearance was obtained. **Results:** Out of 448 subjects 64.1 % were males and 35.9 % were females. Their ages ranged from 18 to 60. Majority (78%) had no baseline comorbidities. All subjects received prophylactic antibiotics, four subjects received oral antibiotics and others (444) intravenous antibiotics. Cephalosporin (90%) was the most frequently used antibiotic. Metronidazole was the most frequently used (80%) additional drug. There was inverse association with number of antibiotics prescribed and presence of co-morbidities ($p=0.002$).Subjects with co-morbidities had a longer mean duration of hospital stay ($p<0.001$). Majority (91.9%) of the subjects continued to receive antibiotics even after 24 hours of surgery. Five (1.1%) subjects developed SSI. **Conclusion:** The core concern of this study was universal prescription of prophylactic antibiotics and the extended duration of the antimicrobial prophylaxis. Due to lack of a standard guideline in India wide variation is seen in selection, duration and dosing of surgical antimicrobial prophylaxis (AMP) across the country and the study highlights the need to formulate and adopt unified guidelines.

KEYWORDS: Antimicrobial prophylaxis, Prescription Pattern, Surgical Site Infections.

BACKGROUND

Infections which occur at the site of incisions are called surgical site infections (SSIs). They are considered to be the most common post-operative complication and second most common cause of nosocomial infections. In India total expenses incurred by patients with SSIs was INR 29,000 (average) as compared to INR 16,000 (average) incurred by non-infected patients.[1,2] In India mean postoperative stay in patients who developed infection was almost four times as compared to patients who did not develop surgical site infection, and the incidence rate was 3.3% to 22.4% for SSI in India.[3] Patients with SSI are 60% more likely to be in an ICU (Intensive Care Unit), and five times more likely to be readmitted to the hospital than those without it.[4] The burden of nosocomial infection is even higher in developing countries like India, as compared to developed countries and SSI are the most preventable types.[5] The administration of empirical antimicrobials preoperatively is one of the measures used to overcome risk of developing SSI after many surgical procedures.[6] So, based on the type of surgery and the microbial flora

present at the surgical site, antimicrobials are used to prevent SSI. There is no adequate information or standard treatment guidelines for surgical antimicrobial prophylaxis in India. These led to concerns of inappropriate use with regard to selection of antimicrobials, timing of administration and duration of prophylaxis.[7] Of greater concern is that almost all the cases are receiving prophylactic antimicrobials irrespective of whether they are indicated or not for prolonged duration against the guidelines.[8] This is mainly attributed to the lack of database on the pattern of use of prophylactic antimicrobials in India. There is a need to generate basic database on the current prescription pattern of prophylactic antimicrobials in institutions all over India so that it can be used for understanding the ongoing trend before any organization can put forward recommendations or provide national guidelines. This study to aims to explore the current prophylactic antimicrobials prescription pattern followed in surgical department in a tertiary care hospital in Karnataka, South India.

MATERIALS AND METHOD

A prospective type study was carried out in the Surgery Department of Justice K S Hegde Charitable hospital, a tertiary care hospital for a period of 12 months from January 2014 to December 2014. Inpatients undergoing surgical procedures in Surgery department during this period were included and their files were reviewed during the post-operative period. Patients between 18 to 60 years of age undergoing elective or emergency surgery were included. Pregnant females were excluded from the study. Informed consents were obtained from the subjects. Data collection was done from the case notes in a specially designed pro-forma about the baseline characteristics, surgical procedure, choice of prophylactic antibiotic, timing of administration, duration and dosage. Each patient was followed up till discharge from hospital. There was no intervention by the investigator in patient's care at any point of time. Institutional ethical clearance was obtained and informed consent was taken from all subjects.

Statistical Analysis

Data obtained were entered into MS Excel sheet and Statistical analysis was done using R software. Results were expressed in rate, ratio and proportion. The Pearson's chi-squared test (χ^2) and Fischer Exact tests were used for finding out association between various categorical variables. Un-paired t test was used to compare days of hospital stay of the subjects. p value < 0.05 was considered statistically significant.

RESULTS

There were 448 subjects in this study of which 288 (64.1%) were males and 161 (35.9%) were females. The age of the patients in this study ranged from 18 to 60 years. Mean age of the participants was 40.04 $\pm$ 11.67 years. Comorbidities were like Diabetes Mellitus, Hypertension, dyslipidemia etc were present among 97 (22%) of subjects. Only one subject (0.2%) had any sort of infection prior to surgery. Majority of the subjects (78.4%) had no baseline co-morbidities. Diabetes Mellitus II was the most common single Co-morbidity affecting 46 (10.2%) subjects. Dyslipidemia was present in 27(6%) subjects. Hypertension was prevalent in 13 (2.9%) subjects. Five (1.1%) subjects were both diabetic (Type II) and hypertensive. Three (0.7%) subjects had malignancies and another three were suffering from various chronic illnesses. All subjects except one were not receiving any antibiotics prior to surgery.

Table No.1 Baseline Characteristics of Subjects.

VARIABLES		N= 448	Percentage
Gender	Male	288	64
	Female	161	36
Age Group	18 – 30	101	22.5
	31 – 40	127	28.3
	41 - 50	119	26.5
	51 - 60	102	22.7

Surgeries were grouped as per ASHP guidelines and Hernia repair constituted of 80(18%) of the surgeries. There were 76(17%) Appendicectomy procedures, 73(16.3%) colorectal procedures, 58(13%) biliary tract procedures, 41(9%) plastic & Breast surgeries and 25(6%) Head & Neck Procedures. Number of Hysterectomy, Gastroduodenal and thoracic procedures among the subjects were three, two and one respectively. Other surgical procedures constituted of 83(18%) of total surgeries.

Table-2: Distribution of study subjects according to pre-operative prophylactic antibiotics received.

Antibiotics	(n=449)	(%)
Ceftriaxone+Sulbactum	185	41.2
Ceftriaxone	70	15.6
Cefotaxime	41	9.1
Cefepime	36	8.0
Ceftriaxone+sulbactam+Metronidazole	35	7.8

Ceftriaxone+Metronidazole	23	5.1
Piparacillin+tazobactam+Metronidazole	9	2.0
Piperacillin+Tazobactum	8	1.8
Ofloxacin+Ornidazole	8	1.8
Cefotaxime+Metronidazole	7	1.6
Amoxycillin+clavulanic acid	6	1.3
Ciprofloxacin	4	0.9
Ciprofloxacin+Metronidazole	3	0.7
Norfloxacin*	4	0.9
Cefoperazone+sulbactam	4	0.9
Imipenem+cilastatin	1	0.2
Cefuroxime+Metronidazole	2	0.4
Cefepime+Metronidazole	1	0.2
Piparacillin+tazobactam+Clindamycin	2	0.4
Total	449	100.0

* by oral route.

Majority of the study subjects, 401(89.3%) received one antibiotic as post-surgical prophylaxis. Two antibiotics were given to 48(10.7%) subjects.

Only 40(8.9%) subjects received post-operative antibiotic prophylaxis within 24 hours of surgery. Majority of study subjects, 406(91.1%) received postoperative antibiotic prophylaxis after 24 hours of surgery.

Table-3: Distribution of subjects according to post surgical prophylactic antibiotics.

Antibiotics	**(n=449)**	**(%)**
Ceftriaxone+sulbactum	164	36.5
Ceftriaxone+sulbactum+metronidazole	88	19.6
Cefepime	36	8
Ceftriaxone+metronidazole	32	7.1
Ceftriaxone	30	6.7
Cefotaxime	26	5.8
Cefotaxime+metronidazole	19	4.2
Piparacillin+tazobactum+metronidazole	11	2.4
Piperacillin+tazobactum	9	2
Ofloxacin+ornidazole	7	1.6
Norfloxacin*	4	0.9
Ceperazone+sulbactum	4	0.9
Cefixime*	4	0.9
Ciplofloxacin+metronidazole	2	0.4
Ciplofloxacin	2	0.4
Cefuroime+metronidazole	2	0.4
Clindamycin+piparacillin+tazobactum+imipenem	2	0.4
Piparacillin+tazobactum+metronidazole+amikacin	2	0.4
Ampicillin+cloxacillin	1	0.2
Amoxycillin+clavulanic acid	1	0.2
Imipenem + cilastatin	1	0.2
Cefepime+metronidazole	1	0.2
Ceftriaxone+sulbactum+metronidazole+ciplofloxacin	1	0.2
Total	**449**	**100**

***** by oral route.

Table 4. Association between Co morbidity status of subjects and number of antibiotics used for surgical prophylaxis

		Number of antibiotics		**P value**
Co-morbidity	Present	One N (%)	Two N (%)	**0.002**
		95 (24)	2 (4)	
	absent	306 (76)	46(96)	

Majority of the study subjects 362(80.8%) were given oral antibiotics after postoperative prophylactic intravenous antibiotic**.** Out of these 362, majority 257(70.9%) were advised to continue oral antibiotics for a few more days after discharge from hospital. Majority of the subjects of the study, 338(86.4%) received one antibiotic as post-surgical prophylaxis. Two antibiotics were given to 56(12.5%) subjects and five (1.1%) received three antibiotics. A total of 14 antibiotics were found to be prescribed in this study either as single antibiotic or in combination. Single antibiotic was given as pre-operative prophylaxis in 401(89.3%) subjects and 48(10.7%) subjects received a combination of two drugs. Eight different combinations of antibiotics were prescribed as pre-operative prophylaxis with highest number of subjects 80(17.8%) receiving Metronidazole as the additional antibiotic followed by 8(1.8%) receiving Ornidazole. Postoperatively intravenous antibiotics were replaced with oral antibiotics in four (0.9%) subjects who received Cefixime after surgery.Duration of Hospital stay of the subjects ranged from one to twenty days, mean duration of hospital stay was calculated to be 4.9 $\pm$ 2.28 days. SURGICAL SITE INFECTIONS**:** Prevalence of SSI in this study was **1.1**%. In these five cases of SSI, culture and sensitivity test of pus from the infection site showed positive for Staphylococcus Aureus for four samples and Escherichia coli bacteria for one. These patients were treated with Chloramphenicol, linezolid and a combination of Imipenem and cilastatin. TIMING OF ADMINISTRATION: Ciprofloxacin and ofloxacin with ornidazole combination were given two hours before surgery whereas all other I.V. antimicrobials were given before one hour. Norfloxacin (4 cases) by oral route was given for colonoscopy with rectal dilatation procedures, but timing of administration was not documented or recorded properly. No intraoperative dosing was done for any procedure as the duration of procedure didn't exceed the half life of the drug given. Out of 449, 333 subjects were given pre-incisional dose 30minutes prior to surgery and the rest 96 subjects were given 1 hour prior to surgery and 13 subjects were given 2 hours prior to surgery. Timings of four patients who were given norfloxacin were not recorded. DOSE OF ANTIMICROBIALS FOR SSI PROPHYLAXIS: Only a few drugs like ciprofloxacin, ceftriaxone, cefotaxime, ampicillin-sulbactum and piperacillin- tazobactum were not given as per recommended dose.

Majority of the study subjects (96%) who were given two antibiotics for pre- surgical antibiotic prophylaxis had no co-morbidities. Subjects with co-morbidities had a longer mean duration of hospital stay of 6.22 $\pm$ 3.14 days when compared to subjects without any co-morbidity who had a mean hospital stay of 4.57 $\pm$ 1.82 days. This difference was found to be statistically significant (p value < 0.001). ORAL ANTIBIOTICS AT DISCHARGE: In this study 369(82.2%) subjects were prescribed oral antibiotics at discharge. Only 80(17.8%) subjects were not prescribed any oral antibiotics in the discharge advice. Majority of the subjects 291(79%) who were prescribed oral antibiotics after the post-operative intravenous antibiotic prophylaxis did not have any co-morbidities (P value <0.607).

DISCUSSION

Majority of the study subjects (64%) were males and similar gender distribution had been reported in many other studies.[7,9,10] This may be due to higher number of hernia repair surgeries in males. Most of the patients belong to the age group 31-40 years and mean age of the participants was 40.04 $\pm$ 11.67 years in this study. This mean age was comparable to those of studies conducted in other parts of the country.[7,9,11] Diabetes Mellitus II was a co-morbidity in 54(12%) subjects which was comparable to its prevalence in a study done in coastal Karnataka.[12] Hypertension was a co-morbidity in 21(4.6%) subjects which is lower than that was shown in another study in coastal Karnataka.[13] In this study, highest number of subjects, 80(17.8%) had undergone hernia repair surgeries followed by appendectomy procedure 76(16.9%). Studies in tertiary care centres in Kerala, New Delhi and Gujarat had also shown similar distribution of surgical procedures.[7,9,11]

All the subjects in this particular study have received prophylactic antimicrobials before procedure, even though systemic antimicrobial prophylaxis is not typically indicated for clean surgical procedures.[14,15,16,17] Only four subjects received oral antibiotics in this study and all others (445) received intravenous antibiotics. In studies conducted in hospitals of New Delhi and Kerala, all the subjects had received systemic antibiotics as pre-operative prophylaxis.[7,9] Parenteral route is preferably suggested for the pre-surgical antibiotic administration because it gives reliable and predictable serum and tissue concentrations.[14] Although Amoxicillin-clavulanic acid, ofloxacin, ofloxacin-orniodazole, norfloxacin, cefepime and cefoperazone were used those are not listed in the guideline, various other studies have shown that these drugs are being used for surgical prophylaxis.[18-25]

Cephalosporin was the most frequently used antibiotic group for pre-operative prophylaxis, it was used in 404(90%) subjects. Out of this, 3rd generation Cephalosporins were the most commonly used antibiotics for this study. A 3rd generation Cephalosporin either alone or in combination was prescribed to majority of the subjects (79.7%) in this study. Ceftriaxone was given as a combination with Sulbactum in 185(41.2%) subjects followed by Ceftriaxone alone in 70(15.6%), Cefotaxime in 41(9.1%). Various other studies in India have shown a similar finding of 3rd generation Cephalosporins, especially Ceftriaxone and Cefotaxime being the most frequently prescribed antibiotics for pre-operative prophylaxis.[7,9,26,27] Many studies from other countries in Asia and other parts of the world also have shown a similar pattern of cephalosporin use.[16, 28-31] Cefepime, a 4th generation cephalosporin was prescribed in 36(8%)

subjects. Some studies have shown the use of cefepime for AMP.[18,25] There are studies showing high usage of cefoperazone as AMP for preventing SSI.[32]

As per SIGN and IDSA guidelines for surgical site infection prophylaxis, it is of paramount importance to select an antimicrobial with narrowest antimicrobial spectrum to decrease emergence of resistance and also because broad spectrum antimicrobials may be necessary if patient develops serious bacteremia later. Therefore it is recommended that the use of Fourth generation or third generation cephalosporins such as ceftriaxone and cefotaxime is inappropriate in SSI prophylaxis.[10] Aminopenicillin was the second most frequently used antibiotic group in this study and it was used in 25(5.6%) subjects. A similar pattern was shown in study conducted by Rehan et al.[9] Further all patients undergoing hernia repair received preoperative antibiotics in this study even though majority (81%) did not have any co-morbidity and underwent elective procedures, while no such prophylaxis is recommended as per SIGN OR IDSA guidelines. A similar pattern of antibiotic use in hernia repair was seen in many other studies also.[7,9]

In this study none of the patients received cefazolin although it is recommended by various guidelines.[14,15,33] In our study a single dose of AMP was given before the surgical procedure, which is in harmony with the various standard guidelines. Previous studies have shown that single dose prophylaxis is not linked with increased rate of SSIs when compared to multiple dose regimens.[34-37]

Metronidazole was the drug frequently used in combination in this study and similar finding was seen in other studies also.[9] Contrary to many other studies wherein Aminoglycosides are commonly prescribed in combination as pre-operative prophylaxis, this study had none who received aminoglycosides.[7,9,10] Majority of the study subjects (96%) who were given two antibiotics for pre- surgical antibiotic prophylaxis had no co-morbidities in this study. This was shown by a Korean study in which they showed irrespective of single or three antimicrobials, patients with cancer as co-morbidity had no influence on SSI outcome.[38] There are some studies that show that routine prescription of prophylactic antimicrobials is not required for patients with diabetes mellitus as comorbidity and having glucose levels under tight control if the same is not indicated for a non diabetic patient having the same condition.[39] Even the guidelines are not recommending to increase the number of antimicrobials according to patient's co-morbidity but indicate these patients are prone for developing SSI. Combination of a number of antimicrobials is infact more influenced by classification of surgical wound and site of surgery.[15,33,34] Association between number of antibiotics prescribed and presence of co-morbidity (p value = 0.002) shows that probably co-morbidity was not the only criterion taken into account for using a combination antibiotic in this study as majority (96%) who received a combination of 2 antimicrobials had no co-morbidity. Other factors like clean, clean-contaminated and dirty procedures as well as site of surgical procedure were probably considered more important. Timing of administration of prophylactic antimicrobials before surgery was according to guidelines in this study. In the Delhi study only 13% of patients received antimicrobials just before surgery.[9] Attaining the right timing and repeat dosing when required are reliant on the operating room staff to follow protocols. Another study by Rakesh Kumar et al shows that antimicrobials were induced just before the surgical incision simultaneously with anaesthesia in 95% cases and in 5% cases it was given 60-120 minutes before surgical incision.[40] Not even one patient in this study received second parenteral antimicrobial doses during surgery as the duration of the procedure had not exceeded the suggested duration. Usually a single dose of the antimicrobial is found to be satisfactory if the length of the surgery is less than four hours or procedure duration is less than two half life of the antimicrobial given and there is no substantial bleeding during the procedure.[41]

Cephalosporins were the most commonly used antibiotic group for post-operative prophylaxis in this study. Among cephalosporins, a 3rd generation drug was mostly prescribed. Aminopenicillin was the second frequently prescribed group and was used in 24(5.3%) cases. Similar pattern of post-operative antibiotic use was demonstrated in other studies also.[12,77] Most commonly used antibiotic post-operatively was Cefotaxime in the Kerala study though in the present study it was ceftriaxone.[12] A fourth generation Cephalosporin, Cefepime was used in 37(8.2%) subjects. Cefepime was not shown to be used commonly for surgical prophylaxis in studies conducted at other centres. A trial in Italy had shown no significant difference in the success rates with the use of Cefepime (4th generation cephalosporin) and ceftriaxone (3rd generation cephalosporin) in preventing surgical site infections.[92] Majority (86.4%) of the subjects received single antibiotic as post-operative prophylaxis followed by 56(12.5%) subjects who received a combination of two antibiotics and 5(1.1%) subjects who received a combination of three antibiotics. Even though the use of combination of two or more antimicrobials may have some sensible reasoning behind it, their indiscriminate use can have several undesirable side effects. Actually the dangerous consequences of such an inappropriate antimicrobial combination could be the emergence of bacteria with antimicrobial resistance, super infection, toxic effects, allergic reactions and increased cost of therapy. Metronidazole was the most frequently used additional drug with 80(17.8%) subjects receiving the same. The subjects who received Metronidazole and Ornidazole continued to receive the same after the procedure as post-operative antibiotics. Similar pattern of Metronidazole was demonstrated in the Kerala Study also.[7] Imipenem, Clindamycin and Amikacin were the other additional drugs used in three drug combinations.The

aminoglycoside Amikacin was one of the additional antibiotics in 2(0.2%) subjects receiving three antibiotic combinations. Many other studies such have shown use of Aminoglycosides as the additional drug in 2 drug and 3 drug combinations for post-surgical prophylaxis.[7,9,10] The Kerala study had shown higher number (24%) of subjects who were replaced with oral antibiotics post-operatively. Cefixime was shown to be the most common drug of replacement in this study and Kerala study.[7]

Similar to most of the prior studies and research indicated, the core concern of this study was the extended duration of the antimicrobial prophylaxis.[2,11,33] Only 40(8.9%) subjects received the postoperative prophylactic antibiotics for less than 24 hours after surgery. Majority (91.9%) of the subjects continued to receive antibiotics even after 24 hours of surgery. Similar extended AMP after surgical procedure was demonstrated in another study.[7] Some other studies show that contrary to the published guidelines that recommend termination of the prophylaxis within 24-48 hours they were extended beyond the recommended period.[29] An extended antimicrobial administration can also be harmful to the patients, as it increases antimicrobial resistance as well as the incidence of the SSI and associated complications.[29] There are also studies that advocate short duration of AMP.[119]

In a study conducted among surgeons, only 8% of surgeons stopped prophylactic antibiotics after 24 hours. Antibiotics were being prescribed for as long as 14 days, which is in total contrast to the norms mentioned in guidelines.[26] In this study 369(82.2%) subjects were prescribed oral antibiotics at discharge and majority among these (79%) did not have any co-morbidities. This injudicious extended prophylactic antimicrobial prescription even after discharge is irrespective of presence of co-morbidity and is not in accordance with standard guideline. Study by Afzal et al had also shown high rate (95.7%) of prescription of oral antibiotics at the time of discharge.[7] Only 5(1.1%) subjects developed Surgical Site Infections in this study. This is much lower than the SSIs observed in other studies. The studies in Gujarat, Gulberga and Delhi had shown an SSI prevalence of 8.6%, 4% and 14% respectively.[9, 10, 11] This disparity could have been due to shorter duration of follow up of patients. Though SSIs are to be ideally assessed till 30 days after the surgical procedure, this study has followed up patients only till their day of discharge and hence the SSIs that developed after the discharge were not taken into account.

All the above results put forward data that says the AMP was obviously overused in this study. It was comparable to the conclusions of several previous studies that noted the overuse as well as misuse of the pre-surgical antimicrobials in India and different parts of the world.[7,9,11,16] A number of measures such as development of local antimicrobial prophylactic guidelines for hospital, increased SSI surveillance, educational interventions, institutional antimicrobial policy, endorsing good surgical techniques and strict aseptic measures in the operating theatre are proposed to prevent the emergence of multidrug resistant organisms. Thorough documentation and flawless entries in the medical records should be promoted and verified so that it will help future studies.

Due to lack of a standard guideline in India wide variation is seen in selection, duration and dosing of surgical AMP. Developing and implementing consensus-based national policy to promote rational use of antimicrobial is on-going due to emergence of multi drug resistant organisms especially that produce NDM enzyme subtypes.[42]

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