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A Drug Utilization Study of Antibiotics in the Cardiothoracic Surgery Department of a Tertiary Care Hospital.

Padma K[1], and Rajathilagam T[2]*.

[1]SRM Medical College Hospital & Research Center, SRM University, Tamil Nadu, India.
[2]ESIC Medical College Hospital & Research Centre, KK Nagar, Chennai, Tamil Nadu, India.

ABSTRACT

Surgical antibiotic prophylaxis plays an extremely vital role in reducing in-hospital mortality. There are very few studies or data in India that document the drug utilization and prescription patterns of antibiotic prophylaxis in cardiothoracic surgery. A prospective cross-sectional study was done for 2 months in the cardiothoracic surgery department of a tertiary care hospital to evaluate the drug utilization pattern of antibiotics in patients undergoing cardiothoracic surgery. The prescription data of 50 patients was analysed in this study.The prescription of antibiotics was as such: the primary prophylactic antimicrobial agents were always given in combination. Post-operatively, these agents were prescribed for 48-72 hours (Period A) followed by a different antibiotic regimen in Period B which lasted for an average of 4.84 days. Third generation cephalosporins(46%)were the most commonly prescribed followed by Fluoroquinolones (33%) and Aminoglycosides (13%).Multiple drug combinations and prolonged antibiotic therapy were the norms in all the cases analysed, with antibiotic prophylaxis lasting upto 5-7 days. In-hospital strategies and local guidelines must be developed to facilitate a more rational prescription of antibiotics in cardiac surgery.

Keywords: antibiotic prophylaxis, aminoglycosides, fluoroquinolones, parenteral antibiotics, prolonged antibiotic therapy, third generation cephalosporins.

Corresponding author

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INTRODUCTION

Surgical Antibiotic Prophylaxis (SAP) plays an extremely vital role in reducing in-hospital mortality.[49]While most surgical departments have a fixed regimen for antimicrobial prophylaxis, wide variations in practice patterns is prevalent in cardiac surgery. [9]Cardiac surgeries differ from other surgical procedures by the use of the cardio-pulmonary bypass. Cardio-pulmonary bypass has been found to compromise humoral immunity, activate white blood cells, and reduce phagocytosis, a possible mechanism for the pre-disposition of cardiac surgery patients to infectious complications.[45] Systemic hypothermia and the longer duration of surgery in cardiac patients increase the risk of surgical-siteinfection (SSI).[46]Added to this that most patients enrolled for cardiac surgery today are of an older age group and have many associated co-morbid conditions like obesity and diabetes mellitus, the risk factors for post-operative nosocomial infections are also higher.[42, 44]

Infectious complications are associated with high morbidity, mortality and economic burden. One common approach has been a long duration of antibiotic prophylaxis, lasting several postoperative days, until all the chest tubes and lines are removed.[18]However, prolonged antibiotic prophylaxis poses the risk of drug side effects, super infection with Clostridium difficile, [38] and the development of resistant bacterial strains. Of these complications, the most significant is the issue of increasing development of resistant bacterial strains, which prolongs hospitalization, and increases mortality and economic burden.[41,47]The rational use of antibiotics has assumed importance, especially in the light of increasing reports of antimicrobial resistance. Guidelines for Surgical Antimicrobial Prophylaxis (SAP) in cardiothoracic surgery has hence been laid down by the Society of Thoracic Surgeons (STS) for choice of antibiotics, duration of dosage and time of first dosage.[1,2]But, recent meta-analyses show that the most applicable regimen still remains open to debate among clinical practitioners.[27, 50]

In the Indian context, studies have shown that the incidence of SSI in cardiac surgery is between 5% and 19%. [36, 37]Since the mortality associated with those acquiring a major infection post-operatively is much higher than those who don't acquire any infection, [42]the antimicrobial regimen adopted assumes special importance. There are very few studies or data in India that document the drug utilization and prescription patterns of antibiotic in cardiothoracic surgery. Our study aims to evaluate the prescribing pattern of antibiotics in pre-operative, intra-operative and post-operative conditions in the cardiothoracic surgery department of a tertiary care hospital.

MATERIALS AND METHODS

Study design

Prospective, observational, cross sectional study.

The study was done for 2 months in the cardiothoracic surgery department of a tertiary care hospitalafter getting approval from the institutional ethical committee.Patients' prescription details were obtained and the details entered in the structured patient profile formafter obtaining verbal informed consent from them.

Inclusion criteria:

All adult patients who were admitted for undergoing surgery in the cardiothoracic surgery department during the study period were included in this study.

Exclusion criteria:

Patients below 18 years of age,those who were continued on prescription from another hospital,patients who were re-admitted for a repeat procedure andthose who were diagnosed with HIV infection and Tuberculosis were excluded from the study.

The collected data was subjected to analysis for:

1) Demographic indicators-Age and Sex

2) Surgical Procedure for which patient was admitted
3) Average number of Drugs/Prescription
4) % of utilization of Different Classes of antibiotics (as per ATC Classification)
5) Antibiotics prescribed per prescription
6) Percentage of fixed dose combinations prescribed- determined by dividing the number of fixed dose combinations prescribed by the total number of drugs prescribed, multiplied by 100.
7) Defined Daily Dose (DDD) of the prescribed antibiotics per 100 bed days.
8) The time of first dosage.
9) Duration of antibiotic prophylaxis.

The antibiotics were classified using the anatomical therapeutic chemical (ATC) Classification System and drug utilization was measured as DDD/100 bed-days, as per WHO recommendations for drug utilization studies.In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Only drugs with an ATC Code can have DDD values. The DDD value in grams of every drug is defined by the WHO and is periodically updated. DDD value of each antibiotic was calculated separately.

DDD= (Number of boxes x Number of tablets in the box or number of vials x Tablets in grams or weight of the vial)/ DDD Value of Antibiotic (in grams).

In this calculation method, the form used for in-bed patients is the ratio of the total DDD per 100 bed days. The index is called the Antimicrobial Consumption Index (ACI).

$$ACI=DDD/bed-days\times100$$

The ABC DDD Calculator (Antimicrobial Consumption Calculator) Version 3.1 developed for the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) was used to calculate the drug consumption rates as meaningful DDD's from hospital pharmaceutical terms. Though the version uses the ATC Classification 2006, it was cross-referenced for changes with the ATC Classification (2013).

Statistical Analysis:

A descriptive statistical analysis was carried out on the data obtained from the study.

- The results on the continuous measurements wereanalysed and depicted as Mean ± S. D
- The results on the categorical data wereanalysed and presented as percentage (%)
- The Chi-Square/ Fischer Exact Test was used to determine the significance of study parameters on the categorical scale between two or more groups.
- Microsoft Office Excel 2007 and IBM SPSS Statistical Package Version 22.0were used to compute and calculate the data.

RESULTS

The prescriptions of 50 patients who underwent cardiac surgery between July and August 2013 were analysed after the application of inclusion and exclusion criteria mentioned above.

58% were male (n=29) and 42% were female (n=21)patients. The mean age of the patients was 46.98 (± S.D 12.52343).

The surgical procedures they were admitted for were analysed and depicted in [**Figure 1]**.48% (n=24) of the patients were admitted to undergo Coronary Arterial Bypass Graft (CABG) and 42% (n=21) were admitted for various valve replacement procedures.

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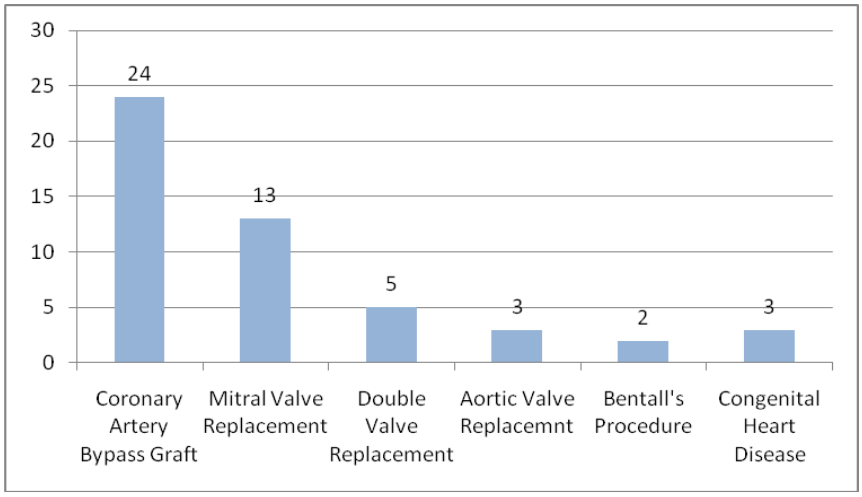

Figure 1: **Type of surgical procedure**

On analyzing the co-morbid factors, the average stay in the hospital was found to be 17.08 days (±S.D= 4.303961).

Primary Prophylactic Therapy

It was observed that the general practice was to combine 2 antimicrobial agents for surgical prophylaxis (consistent with all 50 cases analysed). The choice of antibiotic combinations employed is depicted in [**Figure 2]**. A third generation cephalosporin (cefotaxime or cefoperazone) was combined with either an aminoglycoside (amikacin) or a fluoroquinolone (ofloxacin).

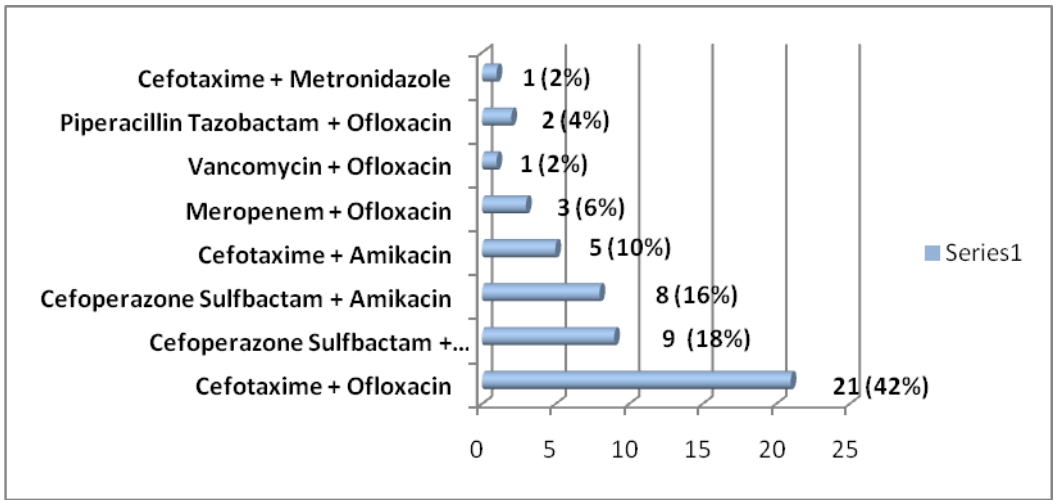

Figure 2: **Choice of antibiotic combinations for surgical prophylaxis**

Table 1: **Antibiotics for surgical prophylaxis**

ATC LEVEL	ATC CLASS	PERCENTAGE OF UTILIZATION
J01DD	Third Generation Cephalosporins	46%
J01MA	Fluoroquinolones	33%
J01GB	Aminoglycosides	13%
J01DH	Carbapenems	3%
J01CR	Beta Lactam Antibiotics	3%
J01XA	Glycopeptide Antibiotics	1%
J01XD	Imidazole Group Antibiotics	1%

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The percentage of utilization of different classes of antibiotics for surgical prophylaxis is depicted in [**Table 1]**. Third generation cephalosporins (ATC Level J01DD) were the most commonly prescribed (46%) followed by Fluoroquinolones (33%) and Aminoglycosides (13%). It is noteworthy that the usage of Glycopeptide Antibiotics (ATC Level J01XA) was very low at 1%.

In all the cases (n=50), the time of first dosage was 60 minutes before first skin incision. This was uniform across all the different classes of antibiotics.

Intra-operatively, no antibiotics were prescribed for any of the patients. The initial prophylactic dosage was not repeated in any of the 50 surgeries.

Prolonged Antibiotic Therapy

All 50 cases studied showed prolongation of the antibiotic prophylaxis.

The duration of antibiotic administration was studied by dividing the post-operative period into two: Period A till the discontinuation of the primary prophylactic agents in 48-72 hours, and Period B in which the prophylactic course was continued for an average period of 4.84 days (±1.03726).

The initial primary prophylactic antibiotics in Period A were prescribed for a period of 48 hours in 50% (n=25), 72 hours in 40% (n=20) and 96 hours in 10% (n=5). The route of administration was intravenous for all the antibiotics prescribed. The choice of antibiotics in Period B forprolonged prophylaxis was analysed and results are depicted in [**Figure 3]**.

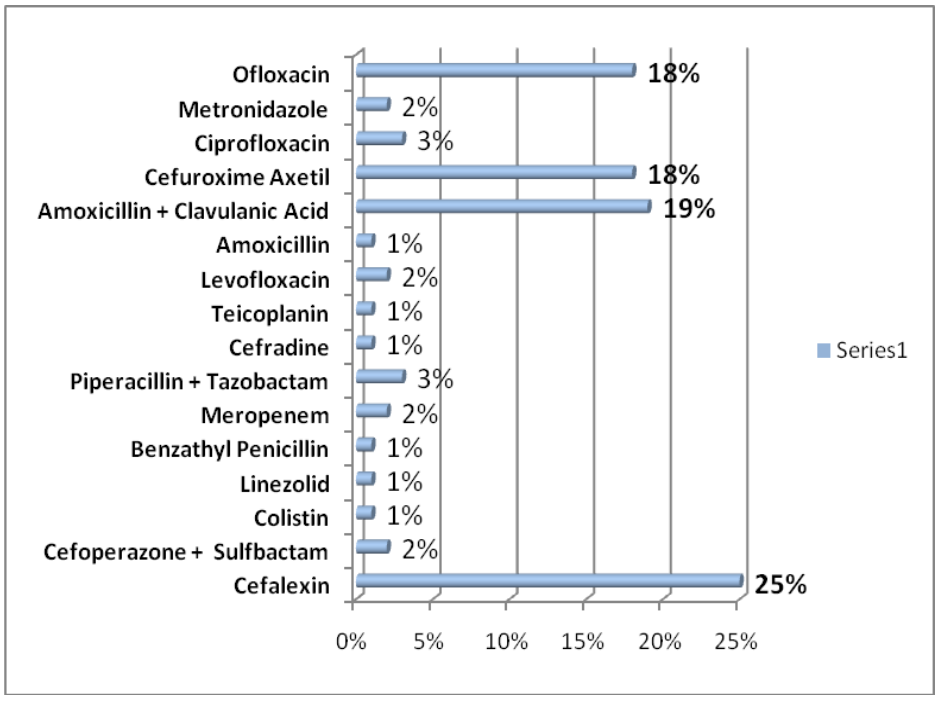

Figure 3: Antibiotics for postoperative prophylaxis

Of these 85% were administered orally and the remaining parenterally. **[Table 2]**

Table 2: Route of administration

ROUTE OF ADMINISTRATION	PERCENTAGE
Oral	85%
Intra Venous	14%
Intra Muscular	1%

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The overall utilization of antibiotics in the surgical prophylaxis of these patients was analysed using the ATC-DDD Method. The results are depicted in **[Table 3]**.

Table 3: Antibiotics utilized for cardiothoracic surgery

ATC CODE	NAME OF ANTIBIOTIC	No. of Grams	No. of DDD's	DDD/100 Bed Days
J01C: Beta-Lactam Antibiotics and Penicillins				**16.0**
J01CR02	Augmentin (Amoxicillin +Clavulanic Acid)	120	120	14.6
J01CR05	Piperacillin + Tazobactam	171	12.2	1.5
J01D: Cephalosporins, Monobactams and Carbapenems				**39.0**
J01DB	First Generation Cephalosporins	117	58.5	7.1
J01DC	Second Generation Cephalosporins	90	180	21.8
J01DD	Third Generation Cephalosporins	274	68.5	8.3
J01GB: Aminoglycoside Antibacterials				**1.9**
J01GB06	Amikacin	16	16	1.9
J01MA: Fluoroquinolones				**20.4**
J01MA01	Ofloxacin (Oral)	24.8	62	7.524
J01MA01	Ofloxacin (Parenteral)	35.2	88	10.680
J01MA02	Ciprofloxacin	8	8	0.971
J01MA12	Levofloxacin	5.0	10.0	1.214
J01XA: Glycopeptide Antibiotics				**0.8**
J01XA01	Vancomycin	5.4	2.7	0.328
J01XA02	Teicoplanin	1.6	4.0	0.485
J01XD: Imidazole Antibiotics				**0.5**
J01XD01	Metronidazole	6.0	4.0	0.5
	TOTAL	908	652.9	**79.2**

A total of 367 drugs were prescribed pre-operatively, of which 2% (ie 6 drugs) were antibiotics prescribed for therapeutic purposes (oral surgery in 4 cases and Urinary Tract Infection in 2 cases)**[Table 4]**. So, no prophylactic dosage was initiated pre-operatively except the single dose before skin incision.

Table 4: Preoperative prescription of drugs

DRUG	Total Number	Average Number Per Prescription	Percentage
Antibiotics	6	0.12	2%
Analgesics	46	0.92	13%
Proton Pump Inhibitors	50	1	14%
Anti Coagulants	49	0.98	13%
Diuretics	30	0.6	8%
***Regular Medications**	186	3.72	51%
***Regular Medications include Anti-Hypertensives, Drugs for Diabetes Mellitus, Angina Pectoris, etc. which the patient consumes regularly.**			

Post-operatively, a total of 673 drugs were prescribed. Of these 152 antibiotics were prescribed at an average of 3.04 antibiotics per prescription (±S. D 0.92494), accounting for 23% of all the drugs prescribed in the post-operative period.**[Figure 4].**

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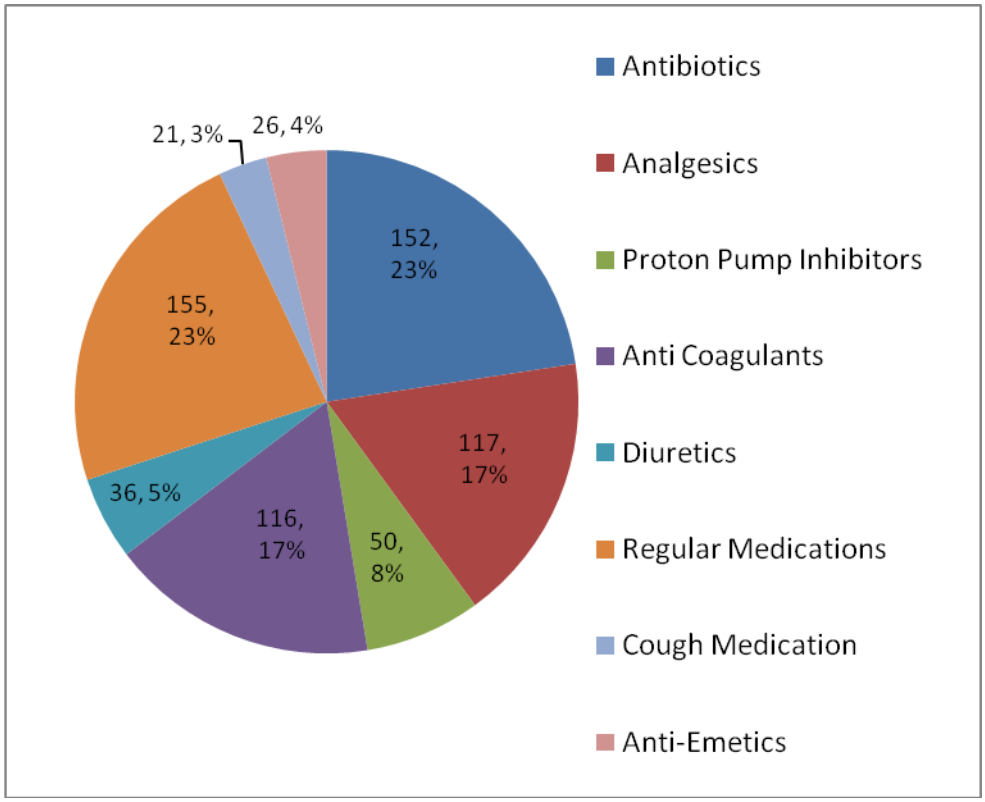

Figure 4: Commonly prescribed drugs in postoperative period

The influence of various co-morbid factors affecting the number of antibiotics prescribed in the post-operative period was analysed. Co-morbid factors include elderly age, female gender, increased number of bed days and diabetes mellitus. The effect of surgical procedure on number of antibiotics prescribed was also studied. More than 2 antibiotics in the post-operative period was prescribed to 84% (21) of those with more than 17 bed days, 76% (16) of the diabetic patients as well as 76%(16) of females admitted and 71% (22) of the elderly patients (calculated as those aged 45 and more). A Univariate analysis was performed to check if any of these factors influenced the number of antibiotics and the results are tabulated in **[Table 5]**.

Table 5: Univariate Analysis of the factors affecting the number of Antibiotics prescribed in patients

Variable	<3 Antibiotics N=13	≥3 Antibiotics N=37	p Value
Age ≥45/<45	9/4	22/15	0.036401
Gender Male/Female	8/5	21/16	0.08822
Bed Days ≥17/<17	4/9	21/16	0.403105
Diabetic Yes/No	5/8	16/21	0.08822
Surgical Procedure (CABG/Valve Procedures)	6/7	18/14	0.179375
Hypertension Yes/No	4/9	8/29	0.002022

DISCUSSION

In the present study, the prescription pattern of the different classes of antibiotics was analysed in a tertiary care hospital.

There was no mortality due to any cause during the period of study. The rate of infection was at 1% with regards to the patients in the study (2 patients enrolled in the study went on to develop infectious complications).

Choice of Antibiotics

The prescription of antibiotics was as such: the primary prophylactic antimicrobial agents were always given in combination (consistent in all 50 cases). Post-operatively, these agents were prescribed for 48-72 hours (designated in our results for convenience as Period A) followed by a different antibiotic regimen in Period B which lasted for an average of 4.84 days (±1.03726).

The most popular antibiotics overall by ATC Class are Second generation Cephalosporins (DDD=21.8, usually oral Cefuroxime axetil), Fluoroquinolones (DDD=20.4, most commonly Ofloxacin), followed by Fixed Dose Combinations of Penicillinsand Beta Lactamase inhibitors (Augmentin: Amoxicillin + Clavulanic Acid, DDD= 14.6). The predominant use of fixed dose combinations is not a good indicator of rational drug utilization.

Guidelines that regulate antibiotic prescription in cardiac surgery, including the Society of Thoracic Surgeons (STS) and the American Heart Association (AHA) advocate the utilization of first generation cephalosporins, usually cephazolin, instead of second and third generation cephalosporins. [1,3] While the prescription of second and third generation cephalosporins may be perceived as not being according to the guidelines, a recent meta-analysis by Ladoret al concluded that second and third generation cephalosporins were as efficacious as first-generation cephalosporins with regard to SSI prevention, and resulted in a lower rate of post-operative pneumonia and lower all-cause mortality. [26]Silveret al showed that newer cephalosporins are more prone to cause antimicrobial resistance and have lesser activity than first generation drugs against Staphylococcus organisms. [32]Englemanet al advocated the first generation cephalosporins as there is no conclusive evidence that second and third generation cephalosporins are more efficacious than the earlier ones in case of SSIs, and considering the economic burden caused by the later cephalosporins. However, the reduction in mortality observed by Ladoret al was probably related to the effect on pneumonia. Rates of pneumonia in these studies were correlated with mortality and previous studies have shown that post-operative pneumonia and ventilator-associated pneumonia (VAP) are strong and significant predictors for death following cardiac surgery, and are not rare events. [28-30]Antibiotic prophylaxis in the critical care setting, even short-duration selective decontamination regimens, results in decreased rates of pneumonia and mortality. [31] Hence, the choice of newer cephalosporins may be justified by the incidence of pneumonia frequently in the ICU setting, however, it was beyond the scope of this study. Further documentation of evidence with regards to comparison among cephalosporins is necessary.

It was observed that the prophylactic antibiotics are prescribed in combinations in all the 50 cases included in the study, usually a second or third generation cephalosporin with an aminoglycoside or a fluoroquinolone. There was no valid clinical or microbiological data available to justify the use of these antibiotics in combination. Englemanet al (Society of Thoracic Surgeons Recommendations) allow the addition of an agent that acts on Gram negative species, but only in the presence of established hospital microbiological data. [1] As there was no clear record of localized gram negative infections in the hospital, nor were there any reports that indicated their absence, further collection of microbiological evidence is recommended in the cardiothoracic ICU and other ICU's in the hospital.

The use of multiple drugs has been reported in studies conducted in Jordan [23] and Australia as well. The Australian study showed prescription of multiple drugs in 58% of cases, and prescription of vancomycin in 68% of cases. [39]However, in the present study, the percentage of prescription of glycopeptides is quite low at 1%. A study conducted in the UK showed that the general practice in present times is to lean towards prescription of glycopeptides in the face of cephalosporin resistance and βLactam allergy. [40]

Time of First Dosage

All the antibiotics were administered 1 hour before skin incision. This is in 100% adherence with the guidelines set forward in the Society of Thoracic Surgeons report by Englemanet al. [2, 27]The importance of the timely administration of pre-operative antibiotics is well established and is broadly applicable to all

procedures for which prophylactic antibiotics are administered. It has been suggested that antimicrobial selection is a moot point if the agent is not delivered during the optimal 30-60 minute window just before incision [2] and that the beneficial effect is negated if the drug is given after incision. [3]

Duration of Antimicrobial Prophylaxis

Use of antibiotics for longer than the recommended period, especially in the absence of any evidence of secondary infection or SSI until the day of discharge in an attempt to preventinfection while patients were hospitalized, was observed in 98% of the study patients and has also been reported by some other researchers in other studies. [23, 33-35]A change in antibiotics course, with the initial prophylactic antibiotic discontinued, and replaced by other antimicrobial agents was also observed. This led to an average of 3.04 antibiotics per prescription. There has been a general move towards the use of shorter courses of antibiotics for surgical prophylaxis in order to reduce toxicity, selection of resistant organisms, Clostridium difficileinfection and cost. [3]Prolonged antibiotic therapy, while not affecting the infection rates, can lead to development of highly resistant strains and put an unwarranted economic burden on the patient, apart from highly affecting morbidity and mortality. [38]

Amongst all the parameters of measuring antibiotic prescription, the prolonged duration was the most commonly frequented deviation. [27] While this has been noted equivocally in studies done in other developing countries [23,33-35]it has also been documented quite frequently in developed nations as well.In a survey among 43 paediatric cardiovascular surgery centres in the United States, up to 76% continued antibiotics while chest tubes were in place. [26] A questionnaire sent to 120 UK cardiac surgeons showed that 28% continued antibiotic use until the removal of all chest drains. [25] In a French survey among 1473 anaesthetists, 23% prescribed >48 hours of antibiotics after cardiovascular surgery. [24]An Australian study documented a lowly 10% concordance rate with international guidelines. [39]This common trend among both developing and developed nations indicate the widespread misnomers regarding prescription of antibiotics, and not just non-adherence to international guidelines.

Further, in this study, no unnecessary pre-operative prescribing of antibiotics was observed. This is in adherence with the guidelines set forward by Englemanet al. [2]There was also no record of intra-operative usage of antibiotics. Guidelines warrant that the prophylactic antibiotics be repeated intra-operatively if duration of surgery exceeds 4 hours. [1,9]However, as our study did not record the duration of surgery, proper analysis could not be done to determine if this practice was in accordance with international norms. But worldwide, it has been noted in many studies that intra-operative re-dosing of antibiotics is missed out quite often, and is one of the deviations from prescribed norms. [23,24,39]

Thus with respect to adherence to international guidelines [1-3, 11-16]it was observed in our study that there were slight discrepancies such as the choice of antibiotics, usage of fixed dose combinations and prolonged antibiotic usage in postoperative period. However, 100% adherence in terms of time of first dosage and an extremely low percentage of utilization of glycopeptide antibiotics are positive signs.

A collection of microbiological evidence and detailed investigations of hospital flora is recommended so that identification of the pathogens will pave way for better and more rational prescribing procedures and can avoid the need for combining antibiotics empirically to cut down infection rates. The way forward can be achieved by forming local hospital strategies and guidelines for antibiotic use, which may be easier to adhere to than an international guideline. Involving an infection specialist and/or clinical pharmacists in the formulation of the same may yield better results. Prolonged antibiotic therapy must be discouraged, and practitioners must be educated about the adverse effects of irrational antibiotic prescriptions, the morbidity and mortality as well as the financial burden associated with it.

CONCLUSION

This study evaluated the utilization of antibiotics in cardiac surgery in a tertiary care hospital over a period of two months. The most common antibiotics prescribed by ATC Classification were in the following order: Second generation cephalosporins, fluoroquinolones, β Lactam antibiotics, Aminoglycoside Antibiotics. Multiple drug combinations were used in all the cases, usually a cephalosporin with a fluoroquinolone, aminoglycoside or β Lactam antibiotics. Prolonged antibiotic therapy was the norm in all the cases analysed,

with antibiotic prophylaxis lasting upto 5-7 days. The low utilization of glycopeptides (1%) and the first dosage being administered 60 minutes before skin incision in 100% of cases were positive findings which adhere with international guidelines. The microbial flora of the ICU and wards attached to the department of cardiac surgery must be studied further, so as to avoid the need to empirically prescribe antibiotics. In-hospital strategies and local guidelines must be developed to facilitate a more rational prescription of antibiotics in cardiac surgery.

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