

Original Article

## USE OF FIXED DOSE COMBINATIONS OF ANTIBIOTICS IN A SURGICAL DEPARTMENT OF A TERTIARY CARE TEACHING HOSPITAL

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### ABSTRACT

**Objective:** To study the prescribing pattern and to assess the rationality of fixed dose combinations of antibiotics in surgical department of a tertiary care teaching hospital.

**Methods:** A cross-sectional prospective study was carried out in four inpatients departments (Surgery, Orthopaedics, ENT, Obstetrics & Gynaecology) of a 550-bed tertiary care teaching hospital. Total 100 inpatients data from all four surgical departments were evaluated for prescribing pattern of fixed dose combinations of antibiotics. Data were also assessed for demographic information like number of single formulations of antibiotics used & fixed dose combinations other than antibiotics.

**Results:** Among four departments, FDCs were prescribed as the highest percentage (20.35%) in the surgery department out of all prescriptions. Maximum median duration of stay was nine days in Orthopaedics. Amoxicillin+Clavulanic acid was the most common FDC prescribed out of all antimicrobials in three departments except orthopaedics. O & G department had maximum percentage (45%) of prescription of Clotrimazole+Tinidazole+Clindamycin, whereas this combination was not prescribed by any of other three departments. Cefoperazone+Sulbactam FDCs were maximally prescribed by surgery department (30.43%) followed by orthopaedics. Diclofenac+Paracetamol and Folic acid combinations were the most commonly prescribed FDC's other than antimicrobials among the subjects.

**Conclusion:** It was observed that the hospital physicians prescribed antibiotics more rationally with no banned drugs and very few new drugs. Rational prescribing of antibiotics would help avoid polypharmacy and prevent drug resistances.

**Keywords:** Antibiotics, Fixed Dose Combination, Surgical departments.

### INTRODUCTION

Fixed dose drug combinations (FDCs), are combinations of two or more active drugs in a single dosage form [1]. Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirement of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance [2]. Rationality of FDCs is on the base of WHO criteria [3, 4]. The Seventeenth WHO Model List of essential medicines (March 2011) contains only 25 approved FDCs whereas the National list of essential drugs of India has 354 essential drugs including 14 FDCs [5]. Still there has been increase in the irrational FDCs in the recent past by leaps and bounds and many of them available as over the counter (OTC) drugs. Unfortunately, many FDCs being introduced in India are usually irrational. The most pressing concern with irrational FDCs is that they expose patients to unnecessary risk of adverse drug reactions.

There are some examples of FDCs, for instance paediatric formulations of nimesulide+paracetamol, diclofenac+ serrato-peptidase, which have increased risk of hepatotoxicity and do not offer any particular advantage over the individual drugs [6]. FDCs of quinolones and nitroimidazoles (e. g. norfloxacin+ metronidazole, ciprofloxacin+tinidazole, ofloxacin+ornidazole) have not been recommended in any standard books, but continue to be heavily prescribed drugs in GI infections, pelvic inflammatory disease, dental infection, etc., to cover up for diagnostic imprecision and lack of access to laboratory facilities [7]. Such injudicious use of antibiotic FDCs can rapidly give rise to resistant strains of organisms, which is a matter of serious concern to the health care situation in our resource poor country.

Various studies indicate that out of total drugs prescribed, 28 to 42 % of the drugs are antimicrobial agents. Around 50 % of these prescriptions of antimicrobial agents are not needed, are inappropriate or are in wrong doses [8].

Such injudicious use of antibiotic FDCs can rapidly give rise to resistant strains of organisms, which is a matter of serious concern to the health care situation in our resource poor country [9].

Quality of life can be improved by enhancing the standards of medical treatment at all levels of health care delivery system. Drugs are one of the most important parts of medical treatment. Because of the important contribution of drugs to the life, use of drugs should be rational. WHO has defined rational use of drugs when "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community"[8]

Prescription study may be helpful to know if there is a problem of irrational use of drugs and to what extent [10].

Keeping this rationale in mind the present study was planned to evaluate the use fixed dose combinations of antibiotics in surgical department of tertiary care teaching hospital.

### MATERIALS AND METHODS

A cross sectional prospective study was carried out at a tertiary care teaching hospital at Kheda district. An ethical clearance was obtained from the institutional ethics committee. Data collected from four surgical departments' i.e. surgery, obstetrics and gynaecology (OBG), orthopaedic and ENT. Due to the short duration of the study and looking to the use of antibiotics in surgery cases only the above mentioned four departments have been selected for the study. There were total of 100 inpatients included in this study. Study was conducted over a period of two months and 25 inpatient prescriptions were scanned per each department to evaluate the prescribing pattern of FDCs antibiotics and their rationality. Data containing antimicrobials of any category were selected randomly irrespective of morbidity, age or sex of the patients or the route of administration of the drug. Demographic detail, morbidity pattern, drug therapy were noted in data collection sheet. Pattern of FDCs of antibiotics, single formulation of antibiotics and FDCs other than

antibiotics were also taken. All the drugs given to the patient during the period of stay in the hospital were noted along with their dose, frequency, route, and the duration. The period of stay of the patient in the hospital was also noted. Descriptive statistics were applied to the collected data using Microsoft Excel software. Results are expressed in percentages.

**RESULTS**

Among four departments, FDCs were prescribed as the highest percentage (20.35%) in the surgery department out of all prescriptions. Prescribed FDCs were 69 (61.06%) and single formulation antibiotics were 44 (38.93%). Out of all prescribed medicines, orthopaedic department had the least numbers of FDCs 4

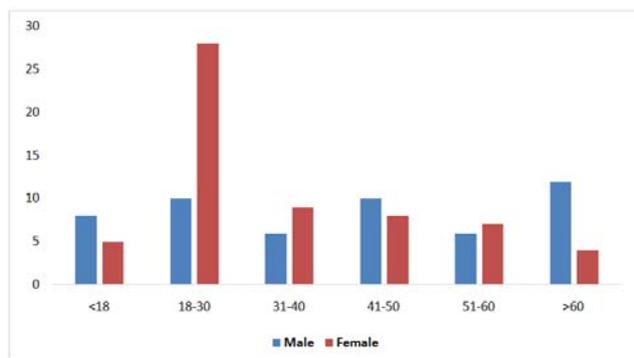
(3.53%) and maximum numbers of single formulation 13 (11.50%) antibiotics [table 1].

Maximum number of subjects among males was from the age group more than 60 y (23.07%) followed by 18-30 y (19.23%) and 41-50 y (19.23%). Maximum number of subjects among the females was from the 18-30 (45.90%) age group. Prescriptions were studied among females were higher (53.98%) than among males (46.02%).11% of total prescription were studied from paediatric age group[fig. 1].

Median duration of stay among three departments i.e. ENT, surgery and O&G was 4 d. Maximum median duration of stay was nine days in Orthopaedics. Highest number of subjects stayed for nine days in the orthopaedic department [table 2].

**Table 1: Department-wise distribution of antimicrobials**

Department	Fixed dose combinations	Single formulations	Total
Surgery	23 (33.33%)	13(29.54%)	36(31.85%)
ENT	22(31.88%)	10(22.74%)	32(28.31%)
OG	20 (28.98%)	8(18.18%)	28(24.77%)
Orthopaedics	4 (5.79%)	13(29.54%)	17(15.044%)
Total	69(61.06%)	44(38.93%)	113
mean±SE	17.25±4.46	11±1.22	28.25±4.09



**Fig. 1: Age distribution**

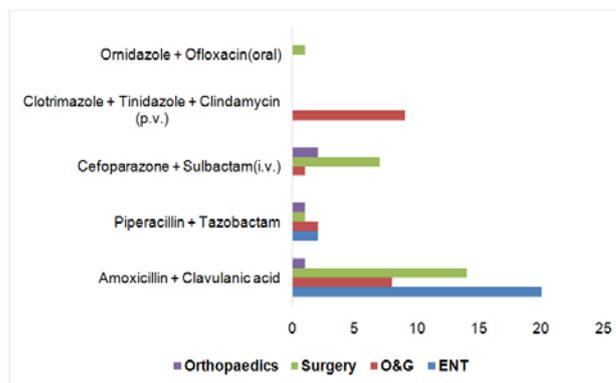
**Table 2: Department wise duration of stay**

Days of stay	ENT	Surgery	OG	Orthopaedics
1-3 D	11	15	13	1
4-6 D	12	14	11	3
6-9 D	1	4	2	3
>9 D	4	2	1	7
Median duration	4	4	4	9.5
mean±S	7±2.318	8.75±2.90	6.75±2.654	3.5±1.089
E	4	2	5	

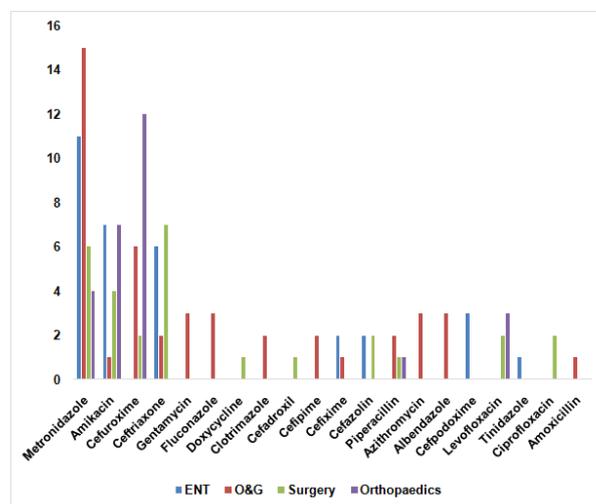
Amoxicillin+Clavulanic acid was the most common FDC prescribed out of all antimicrobials in three departments except orthopaedics. ENT department had maximum percentage (90.90%) of this prescribed combination followed by surgery (60.86%) and O&G (40%) departments. O &G department had maximum percentage (45%) of prescription of Clotrimazole+Tinidazole+Clindamycin, whereas this combination was not prescribed by any of the three departments. Cefoperazone+Sulbactam FDCs were maximally prescribed by surgery department (30.43%) followed by orthopaedics [fig. 2].

Metronidazole was the most common (27.48%) non FDC antimicrobial prescribed in all departments. It was prescribed 36 times in total (oral and intravenous) in the four departments among the subjects. Cefuroxime was the 2<sup>nd</sup> most common antimicrobial

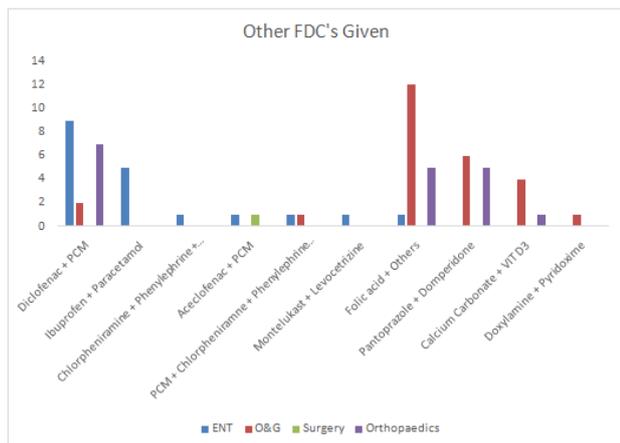
prescribed. Maximum number of non-FDC antimicrobials was prescribed by the O&G department [fig. 3].



**Fig. 2: Department wise distribution of fixed dose combinations of antimicrobials**



**Fig. 3: Department wise distribution of single formulation other than FDCs**



**Fig. 4: Department wise distribution of FDCs other than antimicrobials**

Diclofenac+Paracetamol and Folic acid combinations were the most commonly prescribed FDC's other than antimicrobials among the subjects. Pantoprazole+Domperidone FDCs were most commonly prescribed non antimicrobial FDC by the O&G department. Paracetamol+Ibuprofen FDCs were prescribed only by the ENT department, whereas Doxylamine+Pyridoxime were prescribed only by the O&G department. Out of 133 total FDCs 69 (51.87%) FDCs

were antimicrobial combinations. On the basis of WHO seven point criteria maximum of them were rational [table 3].

## DISCUSSION

Increasing prevalence of infections and the emergence of resistance to antimicrobials has led to polypharmacy with respect to antimicrobial prescription. Antibiotics are considered as the second most prescribed drugs in the world, only next to the drugs indicated for cardiovascular diseases [9]. Fixed dose combinations of antibiotics are highly popular in the Indian pharmaceutical market. Studies showing extensive use of fixed dose of antimicrobials in developing countries. Although there are thousands of fixed dose combinations that are available in the World market. WHO has approved only 25 fixed dose combination in the 15<sup>th</sup> edition of WHO essential drug list [5].

The study was planned to evaluate the use of fixed dose combination and single formulation of antibiotics in surgical department of tertiary care teaching hospital. Use of fixed dose combination of other drugs was also evaluated in this study. Study found that among four surgical departments, maximum use of antimicrobial FDCs was in general surgery department followed by ENT & obstetrics & gynaecology department. Minimum use was in the orthopaedic department. In orthopaedic more use was of single formulation of antibiotics compare to the surgery department. It suggests that infection is very common in this age. Study conducted in Karnataka in 2011, the maximum number of antimicrobial FDC prescriptions (52.17%) was found in surgery outdoor patients, which suggest that use of FDCs of antibiotics is more in surgical departments. Maximum patients were in the age group between 18-30 y of age.

**Table 3: Department wise distribution of fixed dose combination (FDC) of antimicrobials**

FDC's	ENT	O&g	Surgery	Orthopaedics
Amoxicillin+Clavulanic acid	20(90.90%)	8(40%)	14(60.83%)	1(25%)
Piperacillin+Tazobactam	2(9.09%)	2(10%)	1(4.34%)	1(25%)
Cefoperazone+Sulbactam(i. v.)	0	1(5%)	7(30.43%)	2(50%)
Clotrimazole+Tinidazole+Clindamycin (p. v.)	0	9(45%)	0	0
Ornidazole+Ofloxacin(oral)	0	0	1(4.34%)	0
Total	22	20	23	4
mean±SE	4.4±4.3123	4±2.0916	4.6±2.97	0.8±0.4138

**Table 4: FDC-Antimicrobial and other than antimicrobials**

Type of FDCs	Antimicrobial FDCs	Fdcs other than antimicrobial	Total
Numbers of FDCs	69(51.87%)	64(48.12%)	133

It was found that among FDCs of antibiotics Amoxicillin+Clavulanic acid, Piperacillin+Tazobactam and cefoperazone+sulbactam were most frequently used antibiotics. All are parenteral dosage forms. The similar result was found in a study conducted in 2014. In that study, most frequently used FDCs of antibiotics were ceftriaxone+sulbactam, cefoperazone+sulbactam, and amoxicillin+clavulanic acid in respective order.

When two or more drugs are given together as in a fixed dose combination, they may either be indifference to each other or produce synergism or antagonism. When the action of one drug is increased by another drug given concomitantly, it is said to be synergism and when one drug inhibits or decreases the action of another said to be antagonism. The synergistic actions produced by the fixed dose combination drug may remain beneficial for the treatment. Some of the synergistic action of fixed dose combination antibiotics is very much beneficial role in the treatment of infectious disease especially when resistant to single drug treatment is high. In addition, clinically the use of combinations of antimicrobials is advocated for empirical therapy when cause of infection is unknown, for treatment of multiple microbial infections, for synergistic action and to prevent the resistance [11].

One study suggests that there was a favourable clinical response immediately following treatment of the combination of Amoxicillin+Clavulanic acid rather than amoxicillin alone. Piperacillin and

tazobactam is the combination of a fourth-generation, extended spectrum penicillin and a beta-lactamase inhibitor that is used for moderate to severe infections caused by susceptible agents, such as (but not limited to) *Escherichia coli*, many *Bacteroides* and *Klebsiella* species, *Staphylococcus aureus*, and *Haemophilus influenzae*. The combination of piperacillin with tazobactam provides broad activity against beta-lactamase producing penicillin-resistant bacterial species [12].

In O&G department combination of Clotrimazole+Tinidazole+Clindamycin was prescribed by the vaginal route. Several studies have shown that mixed vaginal infections occur frequently. Presence of mixed vaginal infections and bacteria from the rectum that is likely to colonize the vagina is responsible for increased risk of re-infections [13].

Oral and vaginal antimicrobial therapies are the available options for the treatment of bacterial vaginosis, however, the use of oral therapy is constrained by the potential for systemic adverse effects. In clinical practice, local antibiotic therapy is preferred for the routine treatment. Study showed that there favourable clinical responses in majority of the patients treated with the combination of Clotrimazole+Tinidazole+Clindamycin.

Treatment with combination therapy provided prompt onset of relief with regards to the disappearance of clinical indicators of vaginosis. Beneficial effects were exhibited

Within 3 d of study commencement. Complete eradication of infection was noticed in preponderance of patients by day 7 of the study [13].

Ofloxacin and ornidazole in a combined oral dosage form is available in the market. This combination has gained increasing acceptance in diarrhea caused due to bacterial and protozoal infections [14]. Combining Ofloxacin+Ornidazole claimed to be broad spectrum, it is irrational because using this combination adds to cost, adverse effects and may encourage resistance. Study reported combining Ornidazole plus Ofloxacin resulted in serious side effects like allergy, acidity, serious nausea and vomiting in 15 percent of the patients. Present study only one patient has received the combination of ornidazole plus ofloxacin [15, 16].

Metronidazole and Cephalosporin were the most commonly prescribed antimicrobials in single formulation used in this study. Similar finding were shown in previous studies [17, 18]. Aminoglycosides, fluoroquinolones and penicillin were the second most utilized antimicrobials in this study. Two studies found the similar results [19, 20].

Early disease recognition and early start of corrective treatments for such infections were proved to have significant outcomes in terms of treatment effectiveness [21, 22].

The hit and trial method of combining drugs should be replaced by a rational and logical basis for bringing out a fixed dose drug formulation. Sound scientific research should underlie the development and production of drug combinations.

There is a need to carefully monitor and censor misleading claims by the pharmaceutical industry. Clinical pharmacists can play an important role in guiding and imparting knowledge to the public. There is a need to strengthen the mechanism for continuing professional development of practitioners to ensure that they have the necessary knowledge and skills to prescribe rationally.

#### Limitations of the present study

The key limitation of the present study is sample size and duration of study. This study was conducted for the short term student scholarship programme which was approved by the ICMR. Only 100 patients' data was analysed from the surgical department. For decision making of policy for use of fixed dose combinations larger sample size with a longer duration of the study period might be more conclusive. Extensive study by involving other departments is needed for the proper designing of antimicrobial policies and a stringent system for their implementation.

#### CONCLUSION

Total 100 patients analysed from four in-patients from surgical departments. It was found that maximum use of FDC's was by General surgery followed by ENT and O&G. Minimum use was observed by Orthopaedics department. Amoxicillin+Clavulanic Acid, Piperacillin+Tazobactam and Cefoparazone+Sulbactam were the most commonly used FDCs in the study. Only one FDC which was irrational (i.e. Ofloxacin+Ornidazole) was used in one patient by the surgery department. From other FDCs Paracetamol containing FDCs were most commonly prescribed in this study. Maximum FDCs containing Paracetamol were prescribed by the orthopaedics department, that suggests that in this department that use of FDCs containing antibiotics was less and paracetamol containing FDCs were more. The study concluded that fixed dose combinations of antibiotics are prescribed rationally in the surgical department of the tertiary care teaching hospital. Early signals of irrational use of FDCs can be detected by frequent prescription auditing.

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#### CONFLICT OF INTERESTS

Declared None

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