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Antimicrobial utilization pattern in post-operative patients at tertiary care hospital

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Abstract

Drug Utilization Research (DUR) studies are emerging as new tool to keep eyes on irrational prescribing, proper cost utilization and antimicrobial resistance pattern. The present study was planned to evaluate the Daily Defined Dose (DDD), DDD per 100 bed days and Prescribed Daily Dose (PDD) of antimicrobials in post-operative patients using World Health Organization (WHO) / International Network of Rational use of Drugs (INURD) indicators. These indicators give insight of over and under prescription of drug. This was a retrospective observational study conducted in post-operative patients admitted in department of surgery at a tertiary care hospital. Prescribed drugs were classified according to the International Anatomical Therapeutic Chemical Classification System (ATC). Prescriptions of 305 post-operative patients admitted in surgery ward were assessed. Total of 16 antimicrobials prescribed from 7 different classes, 12 (75%) were over prescribed, 2 (12.5%) were adequately prescribed and 2 (12.5%) were under prescribed as per the WHO Daily Defined Dose. All beta lactams were prescribed higher than recommended WHO DDD. Cefuroxime was highest (3 folds) overprescribed antimicrobial. Over and under prescription both lead to resistance. DUR studies on regular intervals will help curb the irrational practice and implementation of health policies.

Keywords: Drug utilization, Defined Daily Dose, Prescribed Daily Dose, Antimicrobial Resistance, Rational Prescribing.

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1. Introduction

Drug utilization research (DUR) is defined by World Health Organization (WHO) as the "marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences. The goal of DUR is to facilitate rational drug use. DUR Studies are useful in identifying irrational prescription, assess the therapeutic and toxic aspects of drugs, provide guidance to solve the problems associated with drug therapy, relate the drug consumption to morbidity pattern and other clinical parameters, determining comparative costs, benefits and indicate the overuse, underuse or misuse of individual drugs or therapeutic classes, promote rational prescription of drugs.[1,2]

WHO developed Anatomical Therapeutic Chemical (ATC), a common global classification system of drugs and Daily Defined Dose (DDD) for drug consumption as reference standard for DUR studies. DDD is average daily maintenance dose of drug for its main indication in adult, whereas Prescribed Daily Dose (PDD) is defined as the average dose prescribed according to a representative sample of prescription.[3] In a nutshell, DDD can be considered as recommended dose unit by WHO for some indication and PDD is actually dispensed unit of drug. The PDD may not always reflect DDD and various studies have shown discrepancies PDD and WHO DDD.[4] Some of the developing countries like Brazil, South Africa, Malaysia have

begun to use the ATC system to enmark their essential drugs and this has eventually lead to preparation of annual drug utilization statistics of the country.[5,6] The DDD is an standard international unit of comparison between two geographically different DUR studies.[7]

The aim of the present study was to evaluate the utilization patterns of antimicrobials in post-operative patients admitted in surgery ward. This is a necessary step to make changes in antimicrobial usage policy of hospital. The results of this study can also be used as baseline to see the effects of drug usage policy implementation effects over the time in same hospital.

2. Materials and Methods

This was a retrospective observational study conducted in the department of Surgery in collaboration with department of Pharmacology at Pt BD Sharma PGIMS tertiary care hospital Rohtak, India. Study was done in accordance with the principles of Declaration of Helsinki and Good clinical practice (ICH-GCP). Approval was taken from Institutional Ethics Committee, PGIMS/UHS, Rohtak before commencement of study.

The prescriptions were studied from case history files of the inward patients. The prescriptions prescribed by physician from post-operative day to the day of discharge were considered. Data collection was done using a predesigned proforma which included patient characteristics such as age, gender, diagnosis, and duration of hospitalization. Prescriptions of post-operative patients between the age of 18-65 years who underwent selective operative procedure were randomly selected. Complicated emergency cases or patient who absconded/left against medical advice and patient who died post-operatively within 24 hours after surgery were excluded from the study. Prescription characteristics such as name of the drugs, strength and dosage form, number of units dispensed were noted.

All drugs were coded as per the WHO ATC/DDD coding system. From the prescription data of antimicrobial drugs, the amounts of drugs consumed were converted into the number of DDD as per the 2010 version of ATC/DDD index. The calculations used for measuring DDD, DDD/100 bed days and PDD were as:

$$\text{DDD} = \frac{\text{Items issued}}{\text{Amount of drug per item}} \textbf{ X } \text{WHO DDD Measure}$$

$$\text{DDD/100 Bed Days} = \frac{\text{Number of DDDs}}{\text{Number of bed days}} \textbf{ X } 100$$

$$\text{PDD} = \frac{\text{WHO DDD measure}}{\text{Number of DDDs}} \textbf{ X } \text{Number of bed days}$$

2.1 Statistical analysis

Data recorded was entered in Microsoft excel 2013 for analysis. For all the descriptive data, Statistical Package for Social Sciences (SPSS) version 23 was used. The data was expressed as numbers, percentages and mean ± Standard Deviation (SD). No statistical hypothesis was tested.

3. Results

A total of 1033 prescriptions were screened between December 2017 to January 2019, out of which 305 post-operative prescriptions were selected based upon inclusion criteria**.** The patients were operated for various indications like cholelithiasis, cholecystitis, various hernia's, appendicitis, cysts, fibroadenoma, abscess, breast cancer etc. The distribution of various inpatients was males (53.8%) and females (46.2%). The mean age of the patients was 42.41±14.46 years. The median duration of hospital stay was 6 days (range 2-28 days).

Average (range) numbers of medicines per prescription were 5.99 (3-13) whereas average number of antimicrobials per prescription was 2.07 (1-6). Antimicrobials were prescribed in all post-operative cases, of these, 103 (33.8%) had single antimicrobial, 117 (38.4%) had two antimicrobial and 54 (17.7%) had three or more antibiotics prescribed. The major classes of antimicrobials prescribed are shown in Table 1.

Table No. 1: Antimicrobials prescribed in surgical post-operative patients with route of administration and ATC code

Drugs	Route	ATC code	Patients(n=305)
Beta lactams			
Ceftriaxone	P	J01DD04	9(2.9%)
Ceftriaxone sulbactam	P	J01DD54	118(38.7%)
Piperacillin-Tazobactam	P	J01CR05	15(4.9%)
Cefixime	O	J01DD08	11(3.6%)
Cefuroxime	O, P	J01DC02	30(9.8%)
Amoxicillin-clavulanate	O, P	J01CR02	221(72.4%)
Cefpodoxime	O	J01DD13	9(2.9%)
Cefotaxime	P	J01DD01	10(3.2%)
Aminoglycosides			
Amikacin	P	J01GB06	73(23.9%)
Streptomycin	P	J01GA01	2 (0.65%)
Quinolones			
Ofloxacin	O, P	J01MA01	36(11.8%)
Levofloxacin	O	J01MA12	3(0.98%)
Antiprotozoal			
Ornidazole	O	P01AB03	16(5.2%)
Oxazolidones			
Linezolid	O	J01XX08	3 (0.98%)
Imidazoles			
Metronidazole	P	J01XD01	76(24.9%)
Sulfonamide			
Cotrimoxazole	O	J01EE01	2 (0.65%)

'O' denotes oral route, 'P' denotes parenteral route

Overall, 2338 DDD's of antimicrobials were utilized in the post-operative surgical patients. Five highly utilized antimicrobials in terms of DDD's were amoxicillin clavulanic acid (796), ceftriaxone sulbactam (573), metronidazole (278), amikacin (185), cefuroxime (148). Comparison of DDD, DDD/100 bed days and PDD is shown in table 3.

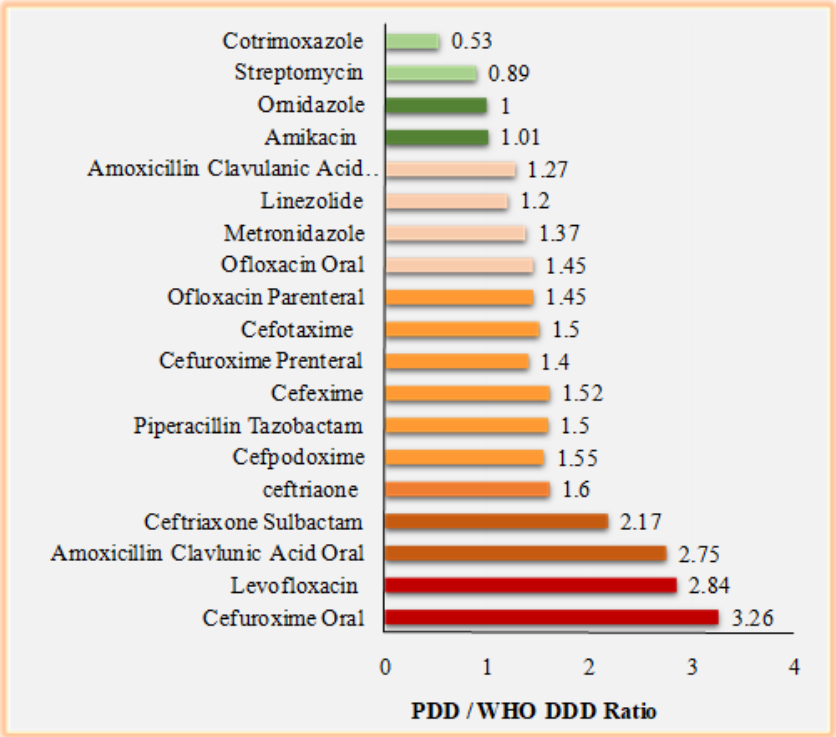
Table 3: Comparison of estimated prescribed daily doses and defined daily doses of various antimicrobials

Class	Drugs	ATC code	Number of DDDs	Number of bed days	DDDs per 100 bed days	WHO DDD	PDD
Beta lactams							
	Ceftriaxone	J01DD04	24	15	160	2	3.2
	Ceftriaxone sulbactam	J01DD04	573	264	217	2	4.34
	Piperacillin-tazobactam	J01CR05	65.3	41	159	14	22.29
	Cefexime	J01DD08	32	21	152	0.4	0.61
	Cefuroxime	J01DC02					
	Oral		134	41	327	0.5	1.63
	Injectable		14	10	140	3	4.2
	Amoxicillin-Clavulanate	J01CR02					
	Oral		538	195	276	1	2.75
	Injectable		258	202	128	3	3.83
	Cefpodoxime	J01DD13	25	16	156	0.4	0.62
	Cefotaxime	J01DD13	15	20	75	4	6
Aminoglycosides							
	Amikacin	J01GB06	185	182	101	1	1.01
	Streptomycin	J01GA01	9.75	11	89	1	0.89
Quinolones							
	Ofloxacin	J01MA01					
	Oral		63	43	146	0.4	0.58
	Injectable		50	34	147	0.4	0.58
	Levofloxacin	J01MA12	20	7	286	0.5	1.42
Antiprotozoal							
	Ornidazole	P01AB03	34	34	100	1.5	1.48
Oxazolidones							
	Linezolid	J01XX08	17	14	121	1.2	1.45
Imidazoles							
	Metronidazole	J01XD01	278	202	137	1.5	2.06
Sulfonamide							
	Cotrimoxazole	J01EE01	3.2	6	53	2	1.06

Beta lactam group alone contributed 71.7% of DDD's, followed by imidazole's 11.8%, aminoglycosides 8.3%, quinolones 5.6%, antiprotozoal 1.4%, oxazolidones 0.7% and sulfonamides 0.1%. DDD/100 bed days show overall consumption of antimicrobial in all hospitalized patients. It does not represent the consumption in individual patient. It is most commonly used to measure the effect of intervention or change in the drug consumption over a period of time.

PDD of a drug is, its average dose unit prescribed in all 305 prescriptions and DDD is WHO recommended dose unit so their ratio demonstrates overuse, underuse or ideal use of any drug. Ratio less than 1 shows underuse; ratio more than 1 shows overuse and equivalent to 1 show the ideal use of any drug. (Figure 1) Difference between PDD and WHO DDD shows the discrepancies between recommended dose and actual prescribed dose.

Figure 1: Ratio of PDD to WHO DDD



The most commonly used antimicrobials were from the beta lactams group and all of them had PDD higher than recommended WHO DDD. Aminoglycosides had the average PDD similar to or lower than WHO DDD, which might be due to narrow safety profile of drugs. All quinolones, metronidazole and linezolid had PDD higher than DDD whereas the same of cotrimoxazole was lesser. Cotrimoxazole was most underused antimicrobial in this study.

4. Discussion

Antimicrobials are daily drivers of surgery department as most of the surgeries require antimicrobials to control pre and postoperative infections. Surgical Site Infections (SSI's) account for 2-40% mortality worldwide and leads to prolonged hospital stay and increased economic burden on the patients.[8] These outcomes of SSI's are more prevalent in developing countries like India due to lack of antimicrobial usage guidelines, limited health services, poverty and lack of education. Developing countries have limited funds available for healthcare and drugs hence it becomes very important to prescribe drugs rationally so that the available funds can be utilized optimally.[9]

Most commonly used antimicrobials in surgical patients of our study were amoxicillin-clavulanic acid (72.4%), ceftriaxone–sulbactam (38.7%), metronidazole (24.9%), amikacin (23.9%), ofloxacin (11.8%). Half of the antimicrobials prescribed were beta lactams. A similar pattern of beta lactam's increasing use was observed in Kotwani *et al.* study which observed change in prescription pattern over 12 months from pharmacy sales and observed that sales of beta lactams had increased by the end of study.[10] Another study by Padma K *et al.*also has shown similar use of antimicrobials where beta lactams were prescribed highest (46%), followed by quinolones (33%) and aminoglycoside (13%) in cardiothoracic surgery patients.[11] Cephalosporins from beta lactam group are the most frequently prescribed drug and that was also observed in various other studies.[12,13] Patel *et al.* from Gujrat also showed cephalosporins (61%) followed by metronidazole (16%) were the most commonly used antimicrobials in ICU [14] however a study from Jamnagar demonstrated that albendazole and cotrimoxazole were prescribed more than any other drug of aminoglycoside and fluoroquinolone group but in pediatric population.[15] This depicts use of class of antimicrobials vary with population and study set up.

Such surplus use of cephalosporins and other beta lactams is easily understandable due to their wide spectrum use and easy availability. Ceftriaxone sulbactam and amoxicillin clavulanic acid were the most commonly used in empirical therapy, to limit gram positive and negative infections. Metronidazole, third highest used antimicrobial in present study, is active against anaerobes, parasites and fungal infection which might be the reason of its extensive use.

Total consumption of antimicrobials in the ward during the study period was interpreted by DDD/100 bed days. In terms of DDD/100 bed days the most consumed antimicrobial groups in hierarchy order, during the study period were beta lactams, quinolones, aminoglycosides, imidazoles, oxazolidones, antiprotozoals and sulfonamides. The values of DDD/100 bed days per say do not possess major practical significance if it is the first DUR study in a particular set up. The results of DDD/100 bed days become of larger interest when there's comparison of before and after intervention or effect of change in regulatory guidelines needs to be measured.

The DDD system is most frequently used in academic research and reports and as a tool for national and international comparison of drug consumption. The DDD consumption in any study depends on types of infection, number of patients and department of study.[16] Amoxicillin clavulanic acid and ceftriaxone sulbactam were the most commonly prescribed beta lactam enzyme inhibitors in our study having DDD 796 and 573 respectively, which is similar as reported by numerous other studies, that assessed changing trends in prescription of beta lactamase enzyme inhibitors and this might be due to its broader spectrum of action, lesser resistance patterns and prescription habits.[17,18] Piperacillin tazobactam is usually kept in reserve for serious infections that is the reason its lesser DDD's were consumed in our study and also in another study of ICU.[12]

Levofloxacin and linezolid were not frequently prescribed in our study hence their DDD accounted for 20 and 17 only respectively. This shows that levofloxacin and linezolid are not preferred in uncomplicated post-operative cases.

DDD consumptions of beta lactam, aminoglycosides were comparable to study conducted by Mittal *et al.* in PGIMER Chandigarh.[19] These studies were conducted in 2 neighboring states and the results were comparable in many aspects.

The use of antimicrobial in the inward patients was assessed by PDD which is other way of expressing drug consumption. The ratio of PDD to WHO DDD was calculated for every antimicrobial to see the extent of its use and this ratio showed that ceftriaxone, ceftriaxone sulbactam, piperacillin tazobactam, cefixime, cefuroxime, amoxicillin clavulanic acid, cefpodoxime, cefotaxime, ofloxacin, levofloxacin, linezolid, metronidazole were overprescribed. Amikacin, ornidazole were adequately used whereas streptomycin and cotrimoxazole were under prescribed.

Our study findings corroborate with Muller *et al.* study done in France on 1,09,410 patients from surgery department and showed beta lactam group antimicrobials were most commonly prescribed drugs. Drug like amoxicillin clavulanic acid, ceftriaxone sulbactam, oral cefuroxime, cefotaxime, metronidazole were found to be overprescribed and cotrimoxazole was prescribed lesser in both the studies.[4]

The average PDD did not correspond to the WHO DDD for many classes of antimicrobials. The WHO DDDs for most anti-infective are based on treatment of moderate infections, however in hospital care, much higher doses are frequently used based upon the severity of infection and requirement of patient.[12] Estimating the usages of antimicrobials is very preliminary step in initiating formulation of drug usage policy in hospital. This study clearly shows discrepancies in recommended doses and prescribed doses of antimicrobials which can augment the resistance and treatment failures.

5. Limitations of Study

The limitation of this study is that it was conducted in one surgical ward only and other surgical wards also should have been investigated, however, this is the preliminary study of its kind in our hospital. Further studies to see the drug utilization pattern in other surgical streams need to be planned.This is an observational study and suffers from the lack of ability to detect unknown confounding factors. DUR studies without culture reporting do not predict the extent of resistance.

6. Conclusion

There is a clear need for the development of standard prescribing guidelines and educational initiatives to encourage the rational and appropriate use of drugs in hospitals. Amendments in antimicrobial prescribing usage policy need to be incorporated in the hospital. More DUR studies in other wards are needed to see the extent of irrational prescribing. The effect of newer prescription guidelines implementation should be measured with repeat study.

Conflict of Interest: None

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