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Prevalence of potential drug-drug interactions in post-operative patients at tertiary care hospital using Lexicomp drug interaction software

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Abstract

Potential drug-drug interactions (pDDIs) contribute to the development of adverse drug reactions, prolonged hospitalization and economic burden of patient. Preventing drug interactions is an important goal to maximize patient benefit from medications. Post-operative patients are very commonly prescribed with antimicrobials, analgesics and gastric acid lowering drugs. These drugs are very prone to have pDDIs. The aim of this study was to find prevalence of pDDIs in post-operative patients using Lexicomp drug interaction checking software. This was a retrospective observational study conducted in 305 patients. The drug interactions were divided into A, B, C, D, X categories with increase in severity from A to X. Total of 130 drug interactions were identified in these 50 prescriptions out of 305. Maximum drug interactions were in category C (48%) followed by category B (23%) and category X (20%). Antimicrobials constituted 52 out of 130 pDDIs. Amongst antimicrobials, category X had maximum (40 %) pDDIs. Many drug interactions can easily be avoided using various drugs interaction software available. According to the results, the use of programs like Lexicomp, for the determination of pDDIs is recommended in the clinical practice in order to prevent avoidable adverse effects.

Keywords: Drug Drug Interactions, Post-operatice Patients, Antimicrobial Utilization, Lexicomp.

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1. Introduction

Potential drug-drug interaction (pDDIs) refers to modification of response to one drug by another when they are administered simultaneously or in quick succession. The modification is mostly quantitative i.e., the response is either increased or decreased in intensity, but sometimes, it is qualitative i.e., an abnormal or a different type of response is produced. The possibility of pDDIs arises whenever a patient concurrently receives more than one drug, and the chances increase with the number of drugs taken.[1]

Drug interactions can be broadly divided into 2 categories of pharmacokinetic and pharmacodynamics interactions. In pharmacokinetics drug interaction there can be changes in absorption, metabolism, alteration in plasma protein binding, volume of distribution, excretion. Enzyme induction and enzyme inhibition can lead to several harmful outcomes like contraceptive failures, antimicrobial resistance, paracetamol toxicity etc. Pharmacodynamic interactions are due to modification at site of action of one drug by another drug, the ultimate effect due to pharmacodynamics interactions can be synergistic or antagonistic. The response can be bizarre sometimes like disulfiram like reaction on taking alcohol when patient is on metronidazole.[2,3]

Hence, it is prudent to consider the possibility of drug interaction whenever two or more drugs are prescribed to a patient. Polypharmacy has become a common practice now, particularly in post-operative cases it is mostly seen that patient is prescribed with antimicrobials, analgesics and gastric acid suppressor drugs. Use of these drugs in post-

operative patients is well justified to control surgical site infections and pain. Antimicrobials are daily drivers of surgery department and most of the surgeries require antimicrobials to control pre and postoperative infections. The mortality due to Surgical Site Infections (SSI) was very high before the start of prophylactic antimicrobials but this prophylactic strategy turned out to be very effective in reducing postoperative infections. These infections increase the health care costs by about 1.5 billion USD/year due to prolonged hospital stay. On an average, the length of patient stay in hospital with post-operative infection is 7 to 10 days longer than others. SSIs are believed to increase the risk of dying 2–11 fold, with 77% of these deaths attributed directly to the infection. Antimicrobials are prescribed usually after surgical procedures to avoid surgical site infections which account for 2-40% mortality worldwide. Surgical site infections prevalence in developing countries is even more.[4,5]

Some antimicrobials have known contraindications as a result of drug interactions and should not be prescribed when these interactions are present. Currently there are electronic platforms available to identify drug-drug interactions like websites and mobile apps. Lexicomp, Micromedex, UW Drug Interaction Database, Up to Date Drug Interactions, Epocrates, First Data Bank, Stockley Drug Interactions, ADME Database (fujitsu), Pharma Pendium (Elsevier) are some examples of such electronic platforms. Lexicomp and Micromedex are proven superior to other ones by various studies. [6] Both these are paid softwares.

This study aimed to evaluate pDDIs in post-operative patients at tertiary care hospital using Lexicomp drug interaction checker. To the best of our knowledge, we could not find study reporting pDDIs in post-operative patients in India hence, this study generated unique data which can help improve quality of prescriptions.

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, Rohtak, tertiary care hospital, in 305 patients. 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 of Pt. BD Sharma PGIMS, Rohtak before commencement of study. Patients of age between 18 to 65 years of either gender, who were operated electively or under emergency condition in general surgery department, were enrolled for this study. Drugs prescribed only post operatively were considered. The case files were selected randomly. Data collection was done using a predesigned proforma. The data was recorded between February 2018 to January 2019, which included the patient demographic details, number, names and dose of all the drugs prescribed, fixed dose combinations, gender, age, surgery details, days of hospitalization etc.

The prescriptions were analyzed for the potential drug interactions using Lexi-Interact™ Online, online software to check drug-drug interactions. Lexicomp is a developer of clinical information solutions. Lexicomp is owned by Wolters Kluwer Company. The company's products include mobile apps, Lexicomp Online, reference handbooks, and desktop software. Lexi-Interact succinctly report the presence or absence of a known interaction along with a risk rating for action (no action needed, monitor therapy, avoid combination, etc.). We checked the drug interactions using Lexi comp mobile application, available by subscription. The risk rating is categorized as A, B, C, D, or X. The progression from A to X is accompanied by increased urgency in the action to be taken. The risk rating categories are described in Table 1. [7]

Table 1: Risk Rating Categories as Presented by Lexicomp for Each Potential Drug-Drug Interaction

Risk Category	Action	Description
A	No known interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents
B	No action needed	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use
C	Monitor therapy	Data demonstrate that the specified agents may interact with each other in clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients
D	Consider therapy modification	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweight the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes or choosing alternative agents.
X	Avoid combination	Data demonstrate that the specified agents may interact with each other in a clinically significant matter. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated

2.1 Statistical Analysis

Data was recorded and entered into a master chart using Microsoft excel 2013. For all the descriptive data, Statistical Package for Social Sciences (SPSS) version 23 was used. All the variables were expressed in number out of total and their respective percentages. The data was expressed as numbers, percentages and mean ± Standard deviation (SD). No particular statistical hypothesis was tested in present study, hence analytical statistics were not applied.

3. Results

3.1 General characteristics

The mean age of the patient was 42.41 ± 14.46 years. Maximum numbers of patients were in the age group 31–50 (45.12%). The number of distributions in the study was comparable in among both the genders. Gall bladder operative procedures accounted for maximum 74 (24.26%) patients. The patients were operated mainly for cholelithiasis and cholecystitis. Hernia patients included inguinal hernia, umbilical and para-umbilical hernia, epigastrichernia, and bubocele were 55 (18%) cases in total. Patients of appendicitis accounted for 45(14.7%) cases. Cysts and different types of nodules like fibroadenoma, lipoma, thyroid cyst, thyroid nodule and scrotal cyst which consisted of 39 (12.78%) patients. Abscess of submandibular region, breast, scrotal, parotid and perianal region accounted for 27 (8.85%) cases. There were 15 (4.9%) cases of carcinoma like carcinoma of breast, thyroid, pancreas, esophagus, gallbladder and lip were included. There were 16 (5.24%) patients who had intestinal obstruction or perforation. Ileostomy patients were 14 (4.5%). In miscellaneous group patients of hydrocele, undescendent testis and renal mass, varicose vein were included. (Table 2)

Table 2: Characteristics of Patients

Gender, n (%)	
Males, n (%)	164 (53.8)
Females, n (%)	141 (46.2)
Age Distribution, n (%)	
18- 30 years	74 (24.3%)
31-50 years	138 (45.12%)
51-65 years	93 (30.5%)
Average age (years)	42.41 ± 14.46
Diagnosis	
Gall bladder disease	74 (24.26%)
Appendicitis	45(14.7%)
Cysts and Nodule	39 (12.78)
Abscess	27 (8.85%)
Others	120 (39.41%)
Duration of Hospitalization	
Maximum duration of hospital stay	27 days
Minimum duration of hospital stay	2 days
Average duration of hospital stay	6.13 ± 2.41 days

3.2 Prescription Analysis

Overall numbers of medicines prescribed were 1827 in 305 prescriptions. Average numbers of medicines per prescription were 5.99 whereas average number of antimicrobials used per prescription was 2.07.

The various classes of antimicrobials used were beta lactams, aminoglycosides, quinolones, antiprotozoals, oxazolidones, imidazoles and sulfonamides. Most commonly prescribed antimicrobial was amoxicillin clavulanic acid, it was prescribed in 221(72.4%) patients. This was followed by ceftriaxone in 118 (38.7%) and metronidazole in 76 (24.9%), amikacin in 73 (23.9%), ofloxacin in 36 (11.9%) patients. Non antimicrobials were prescribed 1193 times in 305 prescriptions, this included proton pump inhibitors, analgesics, multivitamins, antihypertensives, thyroid drugs, anti-emetics and others. Acid suppressing agents 423 (66.7%) and analgesics 76 (11.9%) were most commonly prescribed. (Table no. 3)

Table No. 3: Prescription analysis of post-operative patients

Parameter	Value (n %)
Total prescriptions	305
Total number of medicines prescribed	1827
Total number of antimicrobials prescribed	634
Total number of Non-antimicrobials prescribed	1193
Average number of medicines prescribed per prescription, n (range)	5.99 (3-13)
Average number of antimicrobials per prescription (range)	2.07 (1-6)
Antimicrobials Groups Used	
Beta lactams	423 (66.7%)
Imidazoles (Metronidazole)	76 (11.9%)
Aminoglycosides	75 (11.8%)
Quinolones	41(6.4%)
Others	19 (3.2%)
Non-Antimicrobials Groups Used	
Gastric acid suppressing agents	279 (23.3%)
Analgesics	383 (32.1%)
Antiemetics	37 (3.1%)
Multivitamin and Minerals	156 (13.0%)
Antihypertensive agents	32 (2.6%)
Others	306 (25.6%)

3.3 Categories of Drug Interaction

The DDIs were classified according to their risk category automatically by Lexicomp software upon inserting the details of every prescription individually. Total of 130 drug interactions were identified in these 50 prescriptions. Maximum number of interactions found in one prescription was 5. More than half of the DDI's belonged to category C i.e., monitor therapy. (Table 4, Figure 1)

Figure 1: Number of Patients having Potential Drug Interactions

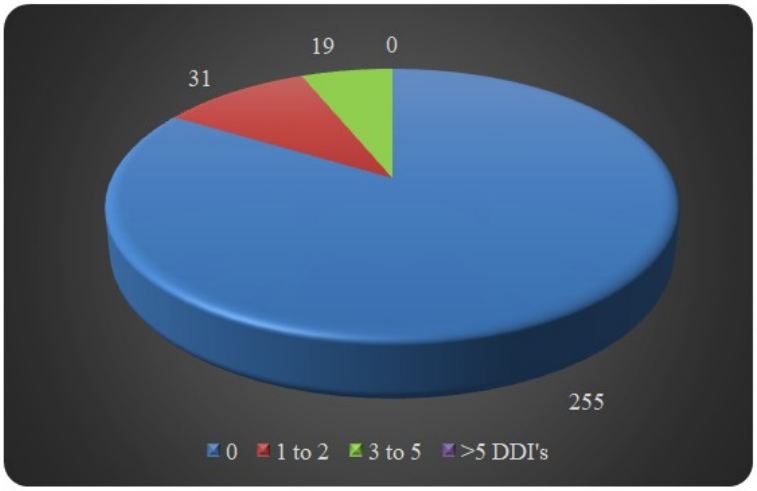

Table No. 4: Number of Potential Drug Interaction in every category

Category of Drug Interaction	Total no. of Interactions (n %)
X	27 (20.7%)
D	10 (7.6%)
C	63 (48.4%)
B	30(23.0%)
A	0(0 %)
Total	130(%)

All the pDDIs were divided in 2 categories of pDDIs with antimicrobial and with non-antimicrobials (Figure 2). Antimicrobials constituted 52 and non-antimicrobials consisted of 78 pDDIs. (Table 5, 6)

Figure 2: Drug Interactions among Antimicrobials and Non-Antimicrobials

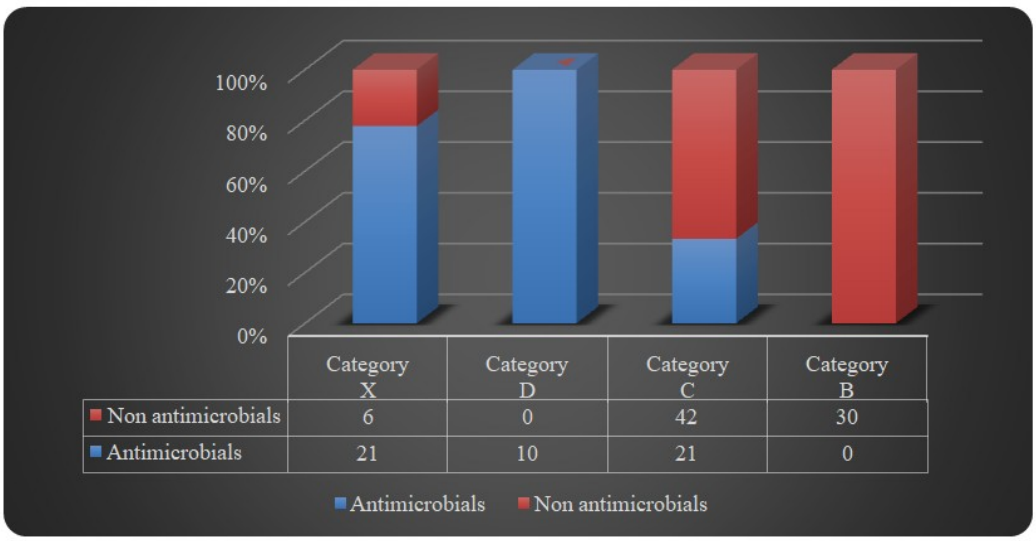

Table 5: Drug Interaction of Antimicrobials

Antimicrobial drug interaction	Total number of interactions (n %)	Category of interaction
Ceftriaxone- Calcium	2 (3.8 %)	D
Cefuroxime -Pantoprazole	12(23.0 %)	X
Cefuroxime- Ranitidine	8(15.3 %)	X
Cefpodoxime-Pantoprazole	5(9.6 %)	C
Cefpodoxime- Ranitidine	3(5.7 %)	C
Streptomycin- Diclofenac	2(3.8 %)	C
Ofloxacin- Aceclofenac	3(5.7 %)	C
Ofloxacin- Calcium	1(1.9 %)	D
Ofloxacin- Multivitamin	7(13.4 %)	D
Ofloxacin- Diclofenac	5(9.6 %)	C
Levofloxacin- Ondansetron	11.9 (%)	C
Linezolid- Ondansetron	1(1.9 %)	C
Linezolid- Metoclopramide	1(1.9 %)	X
Cotrimoxazole- Telmisartan	1(1.9 %)	C
Total	52 (100%)	

Table 6: Drug Interaction of Non-Antimicrobials

Non antimicrobial drug interactions	Total number of interactions	Category of interaction
Aceclofenac -Diclofenac	6(7.6 %)	X
Aceclofenac- Multivitamin	17(21.7 %)	C
Aceclofenac- Telmisartan	4(5.1 %)	C
Tramadol - ondansetron	21(26.9 %)	C
Amlodipine - Diclofenac	3(3.8 %)	B
Liothyronine- Pantoprazole	4(5.1 %)	B
Paracetamol- Metoclopramide	7(8.9 %)	B
Paracetamol- tramadol	16(20.5 %)	B
Total	78 (100%)	

4. Discussion

Surgical patients often develop post-operative surgical site infections. The incidence of SSI in developed countries is 2% but in developing countries it is as much as 40%.[8] This study along with observing the potential drug drug interaction (pDDIs), also observed the drug usage profile of patients undergoing comprehensive range of general surgical procedures. In our study we divided the pDDIs into 2 broad categories i.e. drug interactions with antimicrobials and between non antimicrobials. This categorization will give an insight weather major chunk of drugs interactions points toward cautious use of antimicrobials or non-antimicrobials in post-operative patients. In our study we found total of 130 drug interactions in 50 out of 305 patients. More than 50 % of drug interactions belonged to category C i.e. monitor therapy. These findings are similar to Diaz *et al* who observed prevalence of potential drug–drug interaction risk among chronic kidney disease patients in a Spanish hospital and Kulkarni *et al* who obtained similar results in prescription analysis in a South Indian teaching hospital. Both the above studies concluded moderate drug interactions (monitor therapy) around 70% in their analysis. Antimicrobials constituted 52 pDDI out of 130. [9,10]

In category X, i.e., avoid combination, the antimicrobial drug interaction share was surprisingly high (77%). Most of the category X drug interactions was between cephalosporins and gastric acid reducing drugs. Using cefuroxime together with pantoprazole and ranitidine is not recommended. By reducing stomach acid, these can decrease the absorption and blood levels of cefuroxime and make the medication less effective against infections which can result in higher SSI's and mortality. Cephalosporins like ceftriaxone, cefuroxime and Proton pump inhibitors are very commonly used drugs in post-operative patients which were also noticed in our study. These combinations can sometimes result in serious ADRs like combined treatment with the antibiotic ceftriaxone and the proton pump inhibitor (PPI) can lead to an increased risk of drug-induced arrhythmia, QT syndrome.

Category D i.e., considers drug change, had 10 drug interactions and all were due to antimicrobials. Fluoroquinolones contributed to most of these drug interactions. Most frequent potential antibacterial-drug interactions in category D were found in patients who receive fluoroquinolone antibiotics and multivitamins. The interactions may be avoided, by replacement of fluoroquinolones with safer antibacterials. The package insert

of ofloxacin approved by FDA indicates that mineral supplements, vitamins with iron or minerals, calcium, aluminum or magnesium-based antacids, sucralfate should not be taken within the two-hour period before or within the two-hour period after taking ofloxacin. These agents may substantially interfere with the absorption of quinolones resulting in systemic levels considerably lower than desired.[11] Stuhec *et al* also found fluoroquinolones contributing to major pDDIs.[12]

In both the category X and category D which denote major drug interactions, antibacterials happened to be involved in pDDI. This shows poor practice of antimicrobials usage policy which in long term leads to failure of antimicrobial effect, resistance, increased economic burden on patient and increase in mortality due to SSI. This can be improved with strict hold on antimicrobial usage policy by regulatory agencies.

A Norwegian study reported that antibacterials were not involved in pDDIs and an extensive Scandinavian study in the elderly did not find antibacterials among the 10 most common drug combinations that need dose adjustment, or in the 10 most common combinations that should be avoided because of potential adverse events, which might be related to the fact that Norway for years have had a very strict policy on antibiotics. [13,14]

Amongst non-antimicrobials, only contraindicated combination of drug found was use of aceclofenac and diclofenac together. Diclofenac is the very frequently used NSAID. Its cardiovascular risk profile is of major clinical and public health importance. Diclofenac was found to have a 50% increased rate of major adverse cardiovascular events compared with NSAID non-initiators.[15] Aceclofenac has little pharmacological activity itself; its main mode of action is through its metabolites which include diclofenac and 4'-hydroxy diclofenac. Aceclofenac and diclofenac ultimately lead to formation of same active metabolite after metabolism, which in turn can increase this risk even more. Aceclofenac was involved in 27 out of 78 pDDI of non-antimicrobials, Majority of which were with multivitamins. Vitamin B has shown to increase analgesic effect of NSAID's in post-operative patients but at the same time Vitamin E shows increase in antiplatelet action of NSAID's and risk of bleeding increases.[16] Multivitamins with minerals like zinc are not recommended with NSAIDs. Zinc interacts with NSAIDs and could reduce the absorption and effectiveness of these medications. For the same reason many combinations of multivitamins and minerals are banned in FDC with NSAIDs.[17] Tramadol and ondansetron are very commonly practiced drugs together. Tramadol has established side effect of emesis and ondansetron is prophylactically given to prevent emesis in general practice. Tramadol is a central analgesic dependent on enhanced local serotonergic concentration; ondansetron is a 5-HT_3 selective antagonist. This may result in reduced analgesic efficacy of tramadol and reduced anti-emetic efficacy of ondansetron if these agents are given together.[18]

Minor drug interactions of tramadol which did not require a therapy change were with paracetamol. Both the drugs belong to analgesic group. Interaction between amlodipine and diclofenac was also placed in category B. Diclofenac being an NSAID, can lead to sodium and water retention and decrease in efficacy of antihypertensive agents. Combination of amlodipine and diclofenac was looked for interaction on https://www.drugs.com which is also an online platform for the same. This combination was classified as moderate drug interaction by the above-mentioned website. This interaction could find in place in category C in our opinion in Lexicomp.

5. Conclusion

The prescription review process should be an integral part of hospital policy for detection of potentially inappropriate drug combinations. Our study helped to understand the role of online software in assessing pDDIs. Drug interactions can be easily avoided by taking necessary precautions. Most of the pDDIs can be easily avoided by replacing the drug with other congener that is not associated with drug interactions. Use of technology can help curb the unnecessary prolonged hospitalization due to ADRs, antimicrobial resistance and decrease financial burden of patients and improve the quality of treatment.

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Conflicts of Interest: None

Ethical Approval

The study was approved by Institutional Ethics Committee of Pt. BD Sharma PGIMS Rohtak, Haryana, India.

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