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Research article

Frequency and risk factors of polypharmacy and drug interactions among patients in general intensive care unit of Golestan Hospital, Ahvaz, southwest of Iran

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Abstract: *Objective:* This study was aimed to evaluate polypharmacy and drug interactions in intensive care units. *Materials and methods:* This epidemiologic-descriptive study was performed on the records of 80 patients admitted to the intensive care unit with a duration of more than 48 hours from 2018-10-23 to 2019-01-21. The patients' records, including polypharmacy, type and number of drug interactions as well as factors such as age, gender, hospitalization duration, number of drug-prescribing physicians were investigated. To determine drug interactions, Free *Lexi-Comp iOS* software version 4.0.1 was used. *Findings:* Of 80 participants in this study, 58, and 22 patients (72.5%, and 27.5%) were respectively male and female, with a mean age of 39.9 years; besides, 46.2%, and 25.3% of patients were hospitalized due to trauma, and non-traumatic cerebral hemorrhage, respectively. The average hospitalization was six days. The average number of drug-prescribing physicians and medications received was 5 and 10, respectively. The majority of patients (91.2%) received over five drugs. The majority of drug interactions (70%) were in C-Class, and 1.2% were in X-Class. Also, 85% of the studied samples had at least one drug interaction. *Conclusion:* Polypharmacy and drug interactions were common in patients hospitalized in the intensive care unit ward. Risk factors for increasing drug interactions were the length of stay and number of medications

prescribed, and for polypharmacy, length of stay, number of medications-prescribing physicians, and number of prescription medications.

Keywords: polypharmacy; drug interactions; Intensive Care Unit; risk factor

1. Introduction

One of the concerns of drug delivery today is to identify and minimize drug errors in the medical system. Patients admitted to intensive care units require continuous care and multifaceted remedies, but with increasing severity of disease and changes in organ function as well as the concomitant use of multiple medications, these patients are exposed to more polypharmacy and medication interactions [1,2]. Drug interactions can increase the length of hospital stay, failure of treatment, and increased medical costs [3,4]. Although most drug interactions are preventable, sometimes patients are exposed to important complications and even death [5].

The risk and severity of drug interactions depend on several factors, including the number of prescription drugs, the duration of treatment, the age of the patient, the number of drug-prescribing physicians, and the stage of the disease [6]. Treatment in the intensive care unit (ICU) covers a significant portion of hospital costs and human resources. According to the Kane-Gill study, the amount of medications consumed in the ICU accounts for 38% of the hospital's total medical costs [7,8], and the cost of medication for patients admitted to this ward is equivalent to one night's hospital stay, which doubles the cost of the patient [7,8].

According to the Iranian Ministry of Health and Medical Education, billions of dollars are spent each year on patient care and care due to medication errors, followed by complications of a prolonged stay in hospital [9]. In a study, it was concluded that the annual cost of 29250 dollars will be discounted from indirect costs if one percent of important drug interactions were clinically prevented; because three days will be added to the length of stay of each patient, developing such a drug interaction so that one day will be necessary to identify the drug interaction and two days for deciding on a solution and returning the patient to a normal state [10]. This study aimed to investigate the prevalence of drug interactions and polypharmacy in the ICU in Golestan Hospital of Ahvaz and the ranking of the clinical importance of drug interactions.

2. Materials and methods

A descriptive epidemiologic study was conducted to determine the polypharmacy and drug interactions in patients admitted to the ICU of Golestan teaching hospital of Ahvaz for three months from 2018-10-23 to 2019-01-21.

The inclusion criteria were patient staying longer than 48 hours in the ward and receiving at least two medications simultaneously.

Polypharmacy does not have a single definition globally. Since the large number of studies have reported polypharmacy as taking five drugs [11,12], the present study also considered the use of five drugs or more as polypharmacy. In this study**,** the types of drug interactions were classified as follows: A: no known interaction; B: the drug interaction does not require clinical treatment; C0: drug interactions requiring treatment monitoring, considered by the physician or not monitorable at the time

of the study (for example, monitoring the sedative effects of medications in patients with coma); C1: drug interactions requiring treatment monitoring, missed by the physician); D0: drug interactions requiring dose adjustment, addressed by the physician or not monitorable at the time of study (for example, monitoring the sedative effects of medications in patients with coma); D1: the interactions requiring dose adjustment, missed by the physician; X: drug interaction with the advised category for no concomitant use.

The number and type of interactions were evaluated in terms of severity and classification. Nutritional supplements, serums, electrolytes, PRN drugs, and topical medications were not evaluated. The classification of drug interactions in the studied patients is shown in Table 1.

Table 1. Classification of drug interactions in the studied patients.

Type of drug interaction	Definition
A	No known interaction
B	This drug interaction does not require clinical treatment.
C0	This drug interaction requires treatment monitoring, addressed by the physician or not monitorable at the time of study*.
C1	This drug interaction requires treatment monitoring, missed by the physician.
D0	This drug interaction requiring dose adjustment, addressed by the physician or not monitorable at the time of study*
D1	This drug interaction requiring dose adjustment, missed by the physician

* e. g. monitoring the sedative effects of medications in patients with coma.

2.1. Statistical analysis

The values of quantitative variables (length of hospitalization, the number of visiting physicians, the number of prescription medications, and the number of drug interactions) are expressed as the mean ± standard deviation (SD). The values of qualitative variables (gender, age groups, background disease, and cause disease) are presented as frequencies. The normality of the data was assessed by the Kolmogorov-Smirnov test. The statistical tests such as the Mann-Whitney and the Kruskal-Wallis were used to compare mean values of quantitative variables in the levels of qualitative variables. The association between polypharmacy status and qualitative variables was analyzed using the chi-square test. Also, the association between quantitative variables was analyzed using the Spearman correlation coefficient test. Data were analyzed using SPSS version 18. The P-values of less than 0.05 was considered a significant statistical difference.

3. Results

The demographic and clinical characteristics of enrolled patients was given in Table 2.

Table 2. Demographic and clinical data of the studied patients (N = 80).

Clinical and demographic data	Number (%)
Gender:	
Male	58 (72.5)
Female	22 (27.5)
Diagnoses:	
Traumatic cerebral hemorrhage	35 (43.8)
Non-traumatic cerebral hemorrhage	21 (26.2)
Number of drugs per patient (Mean ± SD)	10 ± 4.1
Length of hospitalization (Mean ± SD)	6 ± 4.1
Number of physicians who prescribed drug to single patient (mean ± SD)	5 ± 2.1

Out of 80 patients admitted in this study, 72.5% (58 patients) were male and 27.5% (22 patients) were female, with a mean age of 39.8 years. In terms of hospitalization, 46.2% and 25.3% were hospitalized due to trauma, and non-traumatic cerebral hemorrhage, respectively. A total to 8.3% due to a brain tumor, 10% due to surgery, 8.8% due to other cases (such as hydrocephalus, aneurysms, cancers, and gastrointestinal bleeding). The average hospitalization duration in these patients was 6.1 ± 4.1 days. The average number of drug-prescribing physicians was 5.0 ± 2.1.

Ten prescription drugs with higher frequency are shown in Table 3.

Table 3. Ten prescription drugs with high frequency.

Medication	Number of Prescriptions (%)	Medication	Number of Prescriptions (%)
Enoxaparin	48 (5.9)	Vancomycin	35 (4.3)
Phenytoin	43 (5.3)	Pantoprazole	30 (3.7)
Bromhexine	43 (5.3)	Levetiracetam	22 (2.7)
Ranitidine	40 (4.9)	Clindamycin	20 (2.4)
Ceftazidime	39 (4.8)	Phenidate	16 (1.1)
Total: 818			

In this study, the total number of prescription drugs in the 80 records studied was 818 drugs among 101 classes. Out of 818 prescription drugs, 400 were injectable drugs. The mean number of medications prescribed for these patients was 10 ± 4.1. At least 2 medications were administered per person at a time, and the maximum number of medications administered was 25 medications at a time.

The frequency and percentage of total interactions detected are shown in Table 4.

Table 4. Frequency and percentage of total interactions detected.

Types of Interactions	Frequency	Percentage
A	3	0.8
B	52	13
C0	118	32
C1	135	38
D0	18	5
D1	28	6
X	4	1.2
Total	358	100

A total of 91.2% of patients received more than five drugs. So, the frequency of polypharmacy was 91.2%, including 43.7% in the case of taking more than ten drugs, 47.5% in the case of taking between 5–9 drugs, and 8.8% in the case of taking between zero to 4 drugs.

The total number of interactions was 358, and the most common interactions were between phenytoin, and ranitidine (Table 5).

Table 5. Frequency of drug interactions in the sample.

Medicinal compound	Frequency	Percentage
Phenytoin and Ranitidine	23	28.8
Enoxaparin and Vitamin E	12	15
Enoxaparin and KCL	8	10
Enoxaparin and Aspirin	6	7.5
Ranitidine and Caco3	6	7.5

A comparison between the number of drug interactions with demographic and clinical information of the patients is shown in Table 6.

Table 6. Comparison between the number of drug interactions with demographic and clinical information of the patients (n = 80).

Variable	P-value
Gender	$Z = -0.24$, $P^{*} = 0.811$
Age	$r = 0.086$, $P^{**} = 0.452$
Length of hospitalization	$r = 0.44$, $P^{**} < 0.001$
Number of visiting physicians	$r = 0.08$, $P^{**} = 0.51$
Number of prescription medications	$r = 0.79$, $P^{**} < 0.001$

*: Mann–Whitney U test; **: Spearman correlation coefficient test.

Results showed a positive significant relationship between drug interactions and the number of days and the number of drugs received (respectively $P < 0.001$ and $P < 0.001$). There was no statistically significant relationship between the number of drug interactions and gender, age, the number of visiting physicians ($P > 0.05$). The mean number of drug interactions in females was equal to 4.86 ± 6.34 and in males was equal to 4.38 ± 4.75. Also, there was no statistically significant difference between number of drug interactions of male and female ($P > 0.05$).

A comparison between polypharmacy status and demographic and clinical information of the patients is shown in Table 7.

Table 7. Comparison between polypharmacy status and demographic and clinical information of the patients (n = 80).

Variable		Polypharmacy		P-value
		Yes (n = 73)	No (n = 7)	
Gender	Male	52 (89.6%)	6 (10.4%)	χ^2 (1) = 0.19, P^*= 0.66
	Female	21 (99.5%)	1 (0.5%)	
Age		40.3 ± 21.3	35 ± 32.5	Z= −0.31, P^{**}= 0.756
Length of hospitalization		6.4 ± 4.1	2.9 ± 1.4	Z = −2.79, P^{**} = 0.005
Number of visiting physicians		6.4 ± 4.1	2.86 ± 1.5	Z = −2.45, P^{**} = 0.014
Number of prescription medications		10.6 ± 4.8	3.71 ± 0.5	Z = −4.36, P^{**} < 0.001
Number of drug interactions		4.9 ± 5.3	0.43 ± 0.8	Z = −3.38, P^{**} = 0.001

*: Chi-square test; **: Mann–Whitney U test.

Results showed that there was a significant statistical difference between mean values of the number of days of hospitalization, the number of visiting physicians, Number of prescription medications and the number of drug interactions in patients with and without polypharmacy (respectively $P = 0.005$, $P = 0.014$, $P < 0.001$ and $P = 0.001$). Also, there was no significant statistical relationship between polypharmacy status and gender, age ($P > 0.05$).

4. Discussion

This study aimed to investigate the prevalence of drug interactions and polypharmacy in the ICU patient and the ranking of the clinical importance of drug interactions. The prevalence of such an event was relatively high.

The prevalence of polypharmacy in our study was 91.2%, In a study conducted in ICUs U.S. Children's Hospitals, 89% of patients were no less than one day exposed to ≥ 5 separate generic medications, and a total of 68.2% of patients were no less than one day exposed to ≥ 10 separate generic medications [13]. In another study, out of 5424 prescriptions studied, 751 (13.85%) had polypharmacy, of which highest rates were seen in the Department of Medicine [14]. These studies also were no in agreement with the present study, which may be due to differences in the characteristics

of the study population, different patterns of drug use, and differences in the treatment process of the patients studied, various study design, sample size and age category.

The frequency of drug interactions in the present study was 43.7%. Four X interactions were found between nimodipine and Phenytoin. Nimodipine is indicated for a variety of conditions in elderly patients because these patients often receive a variety of drugs as treatment [15]. This could be a possible reason for candidating this drug for more prevalent drug interaction and polypharmacy. Besides, phenytoin is a potent enzyme inducer that increases the metabolism of nimodipine and reduces its blood concentration in the body. In this case, nimodipine may not work properly. This interaction may be prevented by technically replacing phenytoin with another drug in the category of antiepileptic drugs [16]. A group of gastric acid neutralizing, preventive, and seizure medications in the intensive care unit. The two drugs also topped the over-the-counter medications. Also, in the study conducted by De Almeida et al., the most widely used ICU drugs, following non-steroidal anti-inflammatory drugs, were anticonvulsants and gastric acid neutralizers. About 75% to 100% of patients admitted to the ward is at risk for gastric stress ulcers, so, prevention of this disorder is performed for most patients at risk. Currently using gastric acid-neutralizing drugs such as ranitidine to achieve this goal is a priority.

Previous studies [17–21] have shown that patients admitted to ICU are more susceptible to drug interactions than other patients due to their clinical status, and the number of medications received [22].

The present study showed that men, women, and different age groups are equally at risk for drug interactions. The present study showed that men, women, and different age groups are at equal risk for drug interactions, which is consistent with the study conducted by Murtaza et al., [23] but in some studies, its prevalence has been more reported in men [16] and in some other studies, it has been more reported in women [6].

In a study conducted by Lima et al., they show different results, suggesting that women and people over the age of 60 years in the ICU are at greater risk of interactions. They have justified that because women make up a greater percentage of their study samples, they are at greater risk of drug interactions than men and that they also report that due to the presence of several problems and the worsening of clinical conditions in people over 60 years of age, they were more likely to receive more drugs, and it, in turn, increases the risk of drug interactions [18].

In this study, there was a significant relationship between the occurrence of polypharmacy and the number of visiting physicians. This can be justified by the fact that patients admitted to ICUs are examined and treated by more specialized physicians due to numerous clinical problems, each of whom may prescribe different medications for patients, which may further the number of medications received and the prevalence of polypharmacy. But there was no significant relationship between drug interactions and the number of physicians, which could be due to the presence of intensivist and their monitoring of services provided [17,24].

There was also a significant association between the prevalence of polypharmacy and drug interactions with a length of stay, which is consistent with the previous studies [20,23,25]. It is natural that patients who were hospitalized longer had a worse clinical condition, needed more treatment. On the other hand, because of their unfavorable clinical condition, they are treated by more physicians and receive more medication, resulting in more drug use and drug interactions.

The results of the present study also showed that as the number of medications prescribed for patients increased, the likelihood of drug interactions increased, which is consistent with previous studies [17–19].

It seems reasonable that the more the received drugs by a patient, the greater the likelihood of drug interactions, so it is advisable to prescribe as few medicines as possible.

5. Conclusion

The results of this study show that the percentage of polypharmacy and drug interactions were high as two important indicators related to drug treatment problems. The frequency of these problems is higher than reported in other studies in Iran.

Risk factors such as length of hospitalization, the number of prescription drugs, interactions, and factors such as length of stay, number of prescription medications, and number of drug-prescribing physicians influenced the prevalence of polypharmacy. Here are some strategies to reduce these problems and their consequences:

(1) If possible, prescribing the least amount of medication and the use of the medicines that have the least number of interactions.

(2) Paying more attention to sensitive groups such as elderly hospitalized patients, and renal and hepatic failure patients

(3) Use of drug interaction identification software

(4) The presence of a clinical pharmacist to reduce drug treatment problems and improve patient conditions

(5) The need to develop guidelines for revising all patients for discontinuation of low-effect or surplus drugs

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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