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Length of intensive care unitstay, number of drugs and drug groups: Independent risk Factors for Potential Drug-drug Interactions: Study in Surgical Intensive Care Unit- Zagazig University Hospitals

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Abstract: Background and Purpose: Drug-drug interactions (DDIs) is frequent in critically ill patients due to polypharmacy, different drug groups and prolonged ICU or hospital stays. The aim of this work was to assess the risk factors for potential drug- drug interactions in surgical ICU patients, Zagazig University Hospitals. **Study design:** Cross-sectional study. **Setting:** Surgical ICUs (SICUs), Zagazig University Hospitals. **Subjects:** We included all patients admitted to SICUs, Zagazig University Hospital for 6 months period, as number of cases with this inclusion criterion at SICUs, ranged from 20-30 per month, so on our study of 6 month on record-based data took files of 120 cases. **Methods:** All patients were subjected to demographic data; age and gender. Clinical history data; main diagnosis, ICU stay in days, transfer from emergency department (ER) or from other departments, mechanical ventilation, previous surgeries, state of consciousness [Glascow coma scale (GCS)], Comorbidities. In hospital medication details: Total number of prescribed drugs in every day of ICU stay had been collected, number of different pharmacological and therapeutic subgroups prescribed and number of physicians who prescribed therapy. Interaction checker data (number and description of the DDI); the presence and classification of DDIs (for every day of the patients, treatment) had been determined by parallel use of two interaction checker data-base: Medscape and Lexi-Interact. **Results:** In the studied population, the age of the studied group ranged from 0.5 to 90 years with mean 43.74 years. Regarding sex 52.5% were male and 47.5% were female. According to Frequency of different Drug interactions among the studied group, 94.2% of the studied group had drug interactions. In Medscape checkers the most frequent interactions among studied group was minor (78.3%), then monitor closely (69.2%), serious (30%) and contraindicated (1.7%). The most frequent interaction in Lexi comp interactions drug checkers was C (monitor therapy) (75.8%), then D (43,3%), B (37.5%), X (8.3%) and A (5%). Total Medscape median 4 interactions per patient with range from 0 to 20. And total Lexi median was 3 interactions per patient with range from 0 to 17. There were +ve significant correlation between number of drug interactions and length of hospital stay, no. of drugs and no. of drugs groups among both Lexi-comp and Medscape interactions. **Conclusion:** To conclude, more than 94% of Patients in ICU usually have Drug drug interaction and this is related to increased number of drugs, drug groups in ICU and length of stay among both Lexi-interactions and Medscape drug checkers. The most frequent interaction in Lexi comp interactions drug checkers was C (monitor therapy) (75.8%) while in Medscape checkers the most frequent was minor (78.3%).

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Keywords: General anesthesia, Drug-drug interaction, Surgical intensive care

1. Introduction

Drug-drug interactions (DDIs) implicate changes in a drug's intended or adverse effects due to recent or concurrent use of another drug or drugs. There are several classifications of drug-drug interactions and one of the most important is the one according to severity: drug-drug interactions could be contraindicated, major, moderate and minor [1].

In order to detect and analyze suspected drug-drug interactions clinicians and researchers nowadays frequently use different computer platforms - personal digital assistant software programs [2]. These computer platforms are in the form of databases which can be updated regularly [3]. There are several online databases for detection and analyzing drug-drug interactions, like Micromedex [4], Lexi-Interact [5], Epocrates [6] or Medscape [7]. However, it is important to note that all of these databases have some shortcomings and discrepancies, especially in regard to classification of interactions according to severity, so it

is advisable to use more than one database for checking drug-drug interactions [2].

Patients in intensive care units (ICUs) usually have severe and life-threatening illnesses so they frequently receive complex pharmacotherapy with large number of different drugs [8]. On average, patients in intensive care unit are receiving 15 different drugs [9], which put them under high risk of drug-drug interactions [10]. Incidence of clinically significant drug-drug interactions in tertiary health institutions in Utrecht, the Netherlands is as high as 54%, whereas average number of interactions per patient is 1.7 [11].

Consequences of drug-drug interactions could be serious, like potentiation of side effects or increase in the toxicity of interacting drugs [9-12]. Drug-drug interactions are responsible for 5%–9% of all adverse drug reactions in hospitalized patients [13]. It is also known that drug-drug interactions contribute to increased morbidity and mortality of patients in ICUs [8].

Drug-drug interactions are more frequent in patients who are elderly, hospitalized for longer period of time, receive more drugs per day [14], and have severe comorbidities [15]. In addition, higher risk for occurrence of drug-drug interactions is noted in patients who are on antithrombotic and/or anticoagulant therapy [16].

Among the identified risk factors for drug-drug interactions in patients of ICUs, large number of prescribed drugs per day, prolonged stay in intensive care unit and pharmacokinetic/pharmacodynamics characteristics of the administered drugs are supported with the largest body of evidence [17-21].

2. Aim of the study:

The primary outcome of the study is detection of the correlation between changes in LAVI under high-dose dobutamine stress echocardiography and the presence of myocardial ischemia and its extent in terms of the number of vessels affected by significant stenosis, as seen by coronary angiography.

3. Patients and Methods

Patents:

This study will include 120 patients admitted to SICUs, Zagazig University Hospital for 6 months period.

Study design:

Cross-sectional study.

Setting:

This study was conducted in surgical ICUs (SICUs), Zagazig University Hospitals.

Target population:

All patients admitted to SICUs, Zagazig University Hospital for 6 months period.

Sample size:

As number of cases with inclusion criteria at SICUs, Zagazig University Hospital ranged from 20-30 per month so on our study of 6 month on record-based data took files of 120 cases.

Inclusion criterion:

All patients admitted to SICUs for 6 months period

Exclusion criteria:

No exclusion criteria.

Methods

Patients were subjected to the following:

Demographic data:

Age and gender.

Clinical history data:

Main diagnosis, ICU stay in days, transfer from emergency department (ER) or from other departments, mechanical ventilation (yes/ no), previous surgeries (yes/no), state of consciousness [Glascow coma scale (GCS)].

Comorbidities:

Dementia or delirium, renal failure, liver cirrhosis, DM, COPD, bronchial asthma, HTN, Heart failure.

In hospital medication details:

Total number of prescribed drugs in every day of ICU stay had been collected, number of different pharmacological and therapeutic subgroups prescribed (anticoagulants, anti-aggregation, anticonvulsants, anti-depressants, antiarrhythmic drugs, analgesics, antibiotics) and number of physicians who prescribed therapy.

Interaction checker data (number and description of the DDI):

The presence and classification of DDIs (for every day of the patients, treatment) had been determined by parallel use of two interaction checker data-base: Medscape and Lexi-Interact.

Ethical approval:

Approval had been obtained from Zagazig University Institutional Review Board (IRB).

Statistical analysis:

Data entry and statistical analyses were performed using statistical package of social sciences (SPSS) version 18. Categorical data were expressed in number and percentage. Continuous normally distributed data were expressed in mean and standard deviation while none-normally distributed data were expressed in median and range.

Inferential statistics carried out using (Chi square, independent t test, Mann-Whitney's U test and Spearman correlation coefficient).

4. Results

In the studied population, the age of the studied group ranged from 0.5 to 90 years with mean 43.74 years. Regarding sex 52.5% were male and 47.5%

were female. The most frequent comorbidities were DM, HTN and cardiac disease.

The mean of duration of hospitalization among the studied group was 7±7.08 days. The most frequent admission causes were post-operative to craniotomy, septic shock, trauma and post-operative observation.

Table (1): Frequency of Drug interactions of different drug checker.

Variable	(n=120) N (%)
Drug interaction:	
No	7 (5.8)
Yes	113 (94.2)
Lexicomp interactions	
A (No known interaction)	6 (5)
B (no action needed)	45 (37.5)
C (Monitor therapy)	91 (75.8)
D (consider therapy modification)	52 (43.3)
X (avoid combination)	10 (8.3)
Total Lexicomp interactions	100 (83.3)
Medescape	
Contraindicated	2 (1.7)
Serious use alternative	36 (30)
Monitor closely	83 (69.2)
Minor	94 (78.3)
Total Medscape interactions	111 (92.5)

The number of prescribed drugs among the studied group ranged from 1 to 14 drugs with mean 8 drugs and mean number of drug group was 5 drugs. Mean number of physicians per day has 4 doctors.

94.2% of the studied group had drug interactions. The most frequent interaction in Lexi -comp interactions drug checkers was C (monitor therapy) (75.8%) while in Medscape checkers the most frequent was minor (78.3%) **(Table 1)**.

Total Lexi interactions per patient were 3.78± 3.63 with median 3 The highest median of interactions per patient in Lexi comp interactions drug checkers among the studied group was C (2), while total Medscape interactions per patient were 4.89 ± 4.26 with median (4) and the highest median of Medscape checkers was minor (2).

There were no differences between cases had drug interactions and cases hadn't in age, sex distribution, frequency of comorbidities, presence of previous surgeries, GCS, diagnosis, site of transfer, number of physicians and mechanical ventilation. But there were statistical significance increase in duration of hospitalization, number of drugs and drug groups in patients had drug interactions, **(Tables 2 – 3)**.

Table (2): Relation between incidence of drug interaction and diagnosis, GCS, main diagnosis, and mechanical ventilation of the studied group:

Variable	No drug interaction (n=7)	Drug interaction (n=113)	P#
LOS (ICU stay): (day)			
Median	2	4	**0.02**
Range	1 - 5	1 - 36	
GCS:			
Median	15	15	0.20
Range	3 - 15	3 - 15	
Variable	**n (%)**	**n (%)**	**P!**
Main diagnosis			
Septic shock	1 (14.3)	20 (17.7)	
Post-operative craniotomy	0 (0)	21 (18.6)	
LL ischemia	0 (0)	4 (3.5)	
Chest infection	1 (14.3)	5 (4.4)	
Stroke	0 (0)	2 (1.8)	
Trauma	1 (14.3)	17 (15)	
Drug over dose	1 (14.3)	1 (0.9)	
SDH	0 (0)	7 (6.2)	
Fits	0 (0)	2 (1.8)	
Post-operative follow up	1 (14.3)	17 (15)	
Post arrest	0 (0)	1 (0.9)	
HELLP	0 (0)	3 (2.7)	
Hydrocephalus	0 (0)	2 (1.8)	0.10
Preeclampsia	0 (0)	2 (1.8)	
Acute pulmonary edema	0 (0)	3 (2.7)	
Hypovolemic shock	2 (28.6)	2 (1.8)	
NSTEMI	0 (0)	1 (0.9)	
Rapid AF	0 (0)	1 (0.9)	
Pulmonary embolism	0 (0)	2 (1.8)	
Transfer from			
Other department	3 (57.1)	84 (74.3)	0.32
ER	4 (42.9)	29 (25.7)	
Mechanical ventilation			
No	3 (57.1)	70 (61.9)	0.32
Yes	4 (42.9)	43 (38.1)	

SD: Standard deviation #: Mann Whitney test!: $\chi 2$ Chi square test

P: significant if <0.05. GCS: Glasgow coma scale, LL: lower limp, AKI: acute kidney injury, SDH: sub-dural hemorrhage, HELLP: hemolysis, elevated liver enzymes, low platelets, NSTEMI: non-ST elevation myocardial infarction, AF: atrial fibrillation, ER emergency room.

Table (3): Relation between incidence of drug interaction and number of drugs prescribed, drug groups, and number of physicians.

Variable	No drug interaction (n=7)	Drug interaction (n=113)	P
Total no of drugs: Median Range	 5 1 - 8	 8 3 - 14	 **0.004#**
Total no of drug groups: Median Range	 4 1 - 6	 5 3 - 10	 **0.03#**
Total no. of physicians: Mean ± SD	 3.57 ± 0.79	 3.86 ± 0.55	 0.19^

N: number, SD: Standard deviation, #: Mann Whitney test, ^: Independent t test, P: Significant <0.05 & highly significant <0.01.

There were +ve significant correlation between incidence of drug interactions and length of hospital stay, no. of drugs and no. of drugs groups among both Lexi comp and Medscape interactions **(Table 4 & Figures 1–3)**.

Table (4): Correlation between number of drug interaction and age, comorbidities, hospital stay, GCS, number of drugs, drug groups, and number of physicians had drug interaction:

Variable	Lexicomp interactions (n=100)		Medescape interaction (n=111)	
	r	P	r	P
Age (years)	0.12	0.26	0.15	0.12
No. of comorbidities	0.04	0.69	0.10	0.28
Length of hospital stay (day)	**0.02**	**0.03**	**0.19**	**0.04**
GCS	0.05	0.62	0.09	0.37
No. of drugs	**0.65**	**<0.001**	**0.60**	**<0.001**
No. of drugs groups	**0.24**	**0.01**	**0.30**	**0.001**
Total no. of physicians	0.05	0.64	0.06	0.50

r: Spearman correlation coefficient, P: Significant <0.05 & highly significant <0.01, No: number

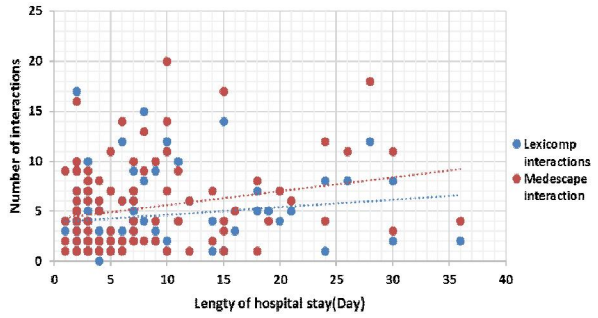

Figure (1): Correlation between number of drug interaction and hospital stay among cases had drug interaction.

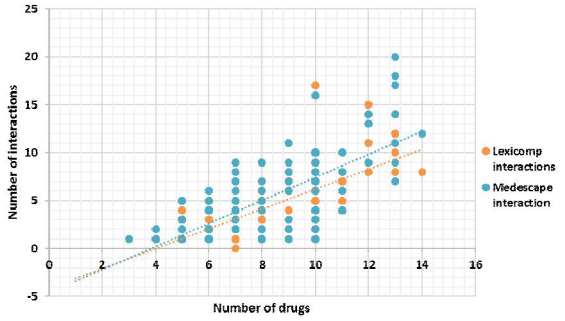

Figure (2): Correlation between number of drug interactions and number of drugs among cases had drug interaction.

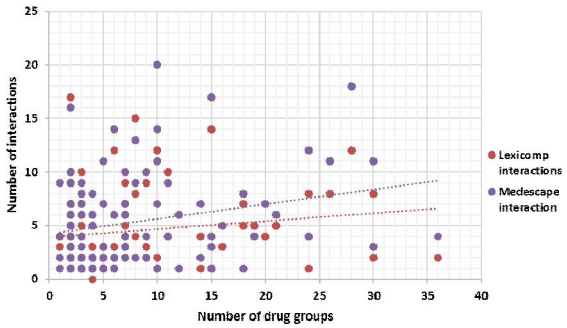

Figure (3): Correlation between number of drug interactions and number of drugs groups among cases had drug interactions.

Using Lexi-comp drug checker, the most frequent interactions were (Acetaminophen & Fentanyl, Phenytoin & Metronidazole, Fentanyl & Midazolam, and Phenytoin & Acetaminophen) in order. Using Medscape drug checker, the most frequent interactions were (Metronidazole & Acetaminophen, Enoxaparin & Acetaminophen, Metronidazole & Phenytoin, and Phenytoin & Zantac).

5. Discussion

This study was planned to assess the risk factors for potential drug- drug interactions in surgical ICU patients in Zagazig University Hospitals. The risk

factors of increased drug-drug interactions were duration of ICU stay, number of drugs and drug groups prescribed for patients.

Similarly, a study was done to assess potential drugs interactions in intensive care patients at a university hospital in Ceará, northeast Brazil, risk factors for drug-drug interactions were length of stay more than 9 days and also number of drugs in those received nine or more drugs. However, they found that age above 60 and female gender are also risk factors which is different from our study. This could be explained by the fact that most patients studied were females those receiving larger number of drugs [23].

Also, in a study that investigated the incidence and related risk factors associated with mutual drug interactions in the neurology wards of two major teaching hospitals in Shiraz, southern Iran. Mutual drug interactions were identified using Lexi-Comp 2012 version 1.9.1. The potential risk factors associated with drug interactions included number of medications and orders, length of hospitalization. But in contrast to our study, other risk factors for DDIs were detected like, patient's age, gender, and the type of neurological disorder as this study concerned about neurology department patients [24].

In a study designed to identify the prevalence of potential drug-drug interactions (pDDIs) in a psychiatric ward, their levels and association with risk factors. This study was conducted in the psychiatric ward of Ayub Teaching Hospital, Abbottabad, Pakistan. Medical records retrospectively reviewed for pDDIs using Micromedex Drug-Reax software. There was significant association of the occurrence of one or more pDDIs with hospital stay of 7 days or longer, taking 7 or more drugs and male gender. In our study the median length of hospital stay is 7.27± 7.2 and the median of total number of drugs were 8.2±2.37 [25].

The aim of a study conducted in the ICU of Imam Husain multispecialty teaching hospital, in Iran to determine whether the frequency of DDIs was associated with ICU length of stay (LOS). The mean LOS was 15.9±16.3 days. The Pearson's correlation method showed that a prolonged ICU stay was positively associated with DDIs [26].

In a retrospective cohort study included 201 patients aimed to determine risk factors for DDIs in ICUs in Kragujevac, Serbia. Three interaction checkers were used to reveal DDIs at ICU patients: Micromedex, Epocrates, and Medscape. This study concluded that the rate of the DDIs in ICU patients adversely influenced by number of drugs or drug groups prescribed per patient, length of hospitalization as approved in our study. However other risk factors not detected in our study were also found, those were antiarrhythmic or anticonvulsant drug prescription, comorbidities, and surgery. On the other hand, presence of cognitive deficit and transfer from emergency department to ICU protect ICU patients from DDIs [27].

In this study, the average number of DDIs per patients was 3 interactions using Lexi comp interactions checker, and 4 interactions per patients using Medscape checker.

Similar average was concluded by Lima and Cassiani as they reported average of three interactions per patient using Micromedex drug interaction checker [23]. Also, Morales-Ríos and colleagues observed that, the prevalence of potential DDIs was 61%, with a median of 4 DDIs per patient using Medscape drug interaction checker [28].

However, the Serbian study was reported from public tertiary hospital, the Average number of DDIs per patient ranged from 10.49 ± 8.80 (Micromedex) to 29.43 ± 21.51 (Medscape) and this average of interactions per patient is higher than this study [27].

Another retrospective cross-sectional study showed that, in a majority cases, 1 - 2 pDDIs per patients were identified with a median of 1 pDDI and this average of DDIs is lower than our study [25].

The most frequent DDIs detected using Lexi comp drug checker were (Acetaminophen & Fentanyl, Phenytoin & Metronidazole, Fentanyl & Midazolam, and Phenytoin & Acetaminophen) in order. Whereas Using Medscape drug checker, the most frequent interactions were (Metronidazole & Acetaminophen, Enoxaparin & Acetaminophen, Metronidazole & Phenytoin, and Phenytoin & Zantac).

In accordance with our results Lima and others identified 311 potential drug interactions, Among the most interacting drugs, midazolam and fentanyl were associated to 45 (14.5%) identified drug interactions [23].

Also, in across sectional study, published in the intensive care society journal, 2013, the highest frequency of interaction occurred between phenytoin and omeprazole [29].

Another study published in journal of critical care, 2018, The most frequent contraindicated/serious/major potential interactions detected by the interaction checkers were showed as follow Epocrates (Midazolam + tramadol (41.3%)), Medscape (Fentanyl + tramadol (24.4%)) and Micromedex (Midazolam + tramadol (41.3%)) in order [27].

Different drug interactions with different combinations could be detected in comparison between this study and other different studies and this may be due to the difference in protocols used in their studies for example, tramadol is not used in our ICUs. Also, the difference in ICU specialties lead to different drugs used with different DDIs.

As in a Pakistani study, a total 27 types of interacting combinations had been identified along with their frequencies. Haloperidol, procyclidine, fluphenazine, promethazine, olanzapine, trihexyphenidyl, fluoxetine, chlorpromazine, divalproex sodium, diazepam and lorazepam were the drugs most commonly encountered in these pDDIs as this study had been done in a psychiatric ward [25].

Another outcome of our study about severity of DDIs as detected with both Medscape and Lexi comp. The most frequent interaction in Lexi -comp interactions drug checkers was type C (monitor therapy) (75.8%), type D (consider therapy modification) (43.3%), type B (no action needed) (37.5%), then type X (avoid combination) (8.3%) in order while in Medscape checkers the most frequent was minor (78.3%), Monitor closely (69.2%), Serious use alternative (30%) then Contraindicated (1.7%) order.

Similar to our study, the result of Iranian study identified DDIs using Lexi comp were that A 4539 drug-drug interactions were detected, including 4118 type C, 403 type D and 18 type X [24].

Different from our study, Morales-Ríos and colleagues used Medscape checker to detect DDIs, the frequency of DDIs based on severity classification was a proportion of 0.2% of potential DDIs was “Contraindicated”, 7.5% were classified as “Serious”, 62.8% as “Significant” and 29.5% as “Minor” [28].

6. Limitations

Results could only be applied on surgical ICU patients (similar population of this study). Another limitation was that using some drug checkers are paid like Lexi-comp interaction checker while others are free like Medscape drug checker.

7. Conclusion

To conclude that, more than 94% of Patients in ICU usually have Drug drug interaction and this is related to increased number of drugs, drug groups in ICU and length of stay among both Lexi-interactions and Medscape drug checkers. The most frequent interaction in Lexi comp interactions drug checkers was C (monitor therapy) (75.8%) while in Medscape checkers the most frequent was minor (78.3%).

Most frequent drug interactions among each type of drug interactions in the studied group were as follow: for Medscape were that the most frequent contraindicated interactions were (linezolid and epinephrine & cordarone and haloperidol), serious interactions was (Fentanyl & Metro-nidazole), monitor closely (Metronidazole & Phenytoin) and finally minor (Metronidazole & Acetaminophen). For Lexi-comp, the most frequent interactions in interactions grade A was (Aspirin & Spironolactone). Grade B was (Acetaminophen & Fentanyl). Grade C was (Phenytoin & Metronidazole). Grade D (Fentanyl & Midazolam). Grade X were (Linozolid & Fentanyl, Ipratropium & K+chloride) respectively.

8. Conflict of interest

The authors declared that there is no conflict of interest.

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