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The effect of different intensivist staffing patterns on the rate of potential drug–drug interactions in adult trauma intensive care units

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Abstract

Background: Drug–drug interactions (DDIs) have created alarming challenges for public health, especially in those admitted to intensive care units (ICUs). Many studies have shown that involvement of intensivists in the ICUs improves the outcome and decreases the treatment costs. The effect of academic *versus* non-academic (therapeutic) intensivist as well as hours of coverage and attendance of intensivist on potential DDIs (pDDIs) was evaluated in six adult trauma ICUs of a level one trauma center.

Methods: In this 6-month cross-sectional study, 200 patients were included. The DDIs were classified into five groups, including type A, B, C, D, and X. pDDIs were defined as interactions belonged to C, D and X categories. Patients in six adult ICUs with three different patterns of intensivist staffing models including type A (once-daily therapeutic intensivist visit followed by 24 h on-call), B (twice-daily academic intensivist visit, 8 h of attendance in ICU and 16 h on-call) and C (all criteria just like ICU type B, except for the presence of therapeutic instead of academic intensivist) were screened for pDDIs.

Results: In total, 3735 drug orders and 3869 drugs (193 different types) were screened and 1826 pDDIs were identified. Type C, D and X interactions accounted for 60.6%, 35.5%, and 3.9% of all pDDIs, respectively. The mean of pDDI per patient was significantly higher (p-value < 0.001) in the ICU type A than ICU types C and B. The frequency of pDDIs was the highest in the type A ICUs. A statistically significant relationship was observed between the number of prescribed drugs and ICU length of stay (p-value < 0.001 and $p = 0.009$, respectively).

Conclusion: Different patterns of intensivist staffing affect pDDIs to varying degrees. In the studied ICUs academic *versus* therapeutic intensivist, twice *versus* once-daily visit, and 8 h attendance with16 h on-call *versus* 24 h on-call were associated with more reductions in pDDIs.

Keywords: drug–drug interactions, ICU staffing, risk factor, the intensive care unit

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Plain language summary

The impact of different intensivist staffing patterns in ICUs on the rate of potential drug-drug interactions

Drug-drug interactions (DDIs) have created alarming challenges for public health, especially in patients admitted to intensive care units (ICUs). Many studies have shown that involvement of

intensivists in the ICUs improves the outcome and limits the costs. Considering the high incidence of potential DDIs (pDDIs) occurring for critically ill patients and the importance of ADRs caused by pDDIs in ICUs, the effect of the presence of an academic versus therapeutic intensivist, as well as the hour of coverage of intensivist on prevalence of pDDIs was evaluated in six adult trauma ICUs of a level one trauma center in Shiraz, Iran. We also determined the prevalence of pDDIs and their associated risk factors. To the best of our knowledge, this is the first study that has assessed the effect of various ICU physician staffing models on the incidence and pattern of pDDIs.

Introduction

The patient safety, as one of the basic concepts in healthcare systems, has received extensive attention during recent years.[1] An adverse drug event (ADE) is defined as expected or unexpected side effect of an administered drug, while medication error (ME) can cause ADEs.[2] The Institute of Medicine in its 2006 report, *Preventing Medication Errors*, stated that more than 1.5 million preventable ADEs occur every year in the United States and considered reducing ADEs and MEs as top national priorities.[3]

Drug interaction (DI) is a type of adverse drug reaction (ADR) that occurs when the effect of one drug is changed by another agent including drugs (drug–drug interactions or DDIs), food, herbal and other substances, and results in qualitative or quantitative alteration in the drug action.[4,5] It is estimated that DDIs account for 3–26% of hospital admissions caused by ADRs.[6] It was reported in a review article that ADRs due to DDIs cause 0.05% of the emergency department visits, 0.6% of the hospital admissions and 0.1% of the rehospitalizations.[7] Thus, DDIs are considered as a clinical and public health concern.[8] A potential DDI (pDDI) occurs when two drugs known to interact are co-prescribed, and thus it is anticipated that DDI occurs in the exposed patient.[9] Critically ill patients in the intensive care unit (ICU) are more vulnerable to DDIs due to altered absorption and metabolism, renal complications and, most importantly, polypharmacy.[10,11] It seems that DDIs are twice as likely to occur in ICU patients compared with patients in other wards.[12] According to the review of literature, MEs occur at a median rate of 106 per 1000 ICU patient-days.[13,14] It is thought that pDDIs are associated with increased mortality, as well as morbidity in ICU patients.[15] Several risk factors have been proposed for the occurrence of DDIs, including the demographic characteristics of the patients (e.g. age), length of treatment and hospital stay, number of administered drugs, stages of disease, concurrent diseases such as shock, renal failure, and liver diseases, such as cirrhosis and acute viral hepatitis.[16]

A wide variety of ICUs exist based on ICU organization, in particular the physician staffing.[17] The Society for Critical Care Medicine published a guideline in 2001 emphasizing the important role of intensivists in delivery of critical care in ICUs. It recommended that patient care should be provided by intensivists leading multidisciplinary groups dedicated to the ICU.[18] The intensivists are skillful at treating critically ill patients and are immediately available to treat their complications, so they are able to reduce morbidity and mortality. Furthermore, intensivists can decrease resource use by decreasing unnecessary ICU admissions, prompting discharges and preventing complications that prolong the ICU length of stay.[19] Despite the beneficial role of intensivists in the ICUs, only 10% of ICU patients have the chance to be treated by a dedicated intensivist-led multiprofessional team. Annually, 162,000 preventable deaths occur in the United States of America due to lack of presence of intensivists in the ICUs.[20] According to the evidence, interprofessional care, the care provided by a team of healthcare professionals, including intensivists, critical care nurses, advanced practice providers, pharmacists, respiratory care practitioners, rehabilitation specialists, dieticians, social workers, case managers, spiritual care providers, intensivists, and non-intensivist physicians can improve multiple patient level outcomes, particularly in patients with increasing complexity and medical comorbidities.[21]

Considering the high incidence of pDDIs in the ICU, and the importance of ADRs caused by pDDIs in critically ill patients, we aimed to investigate the effect of the presence of academic *versus*

therapeutic intensivists as well as the hour of coverage of intensivist on pDDIs in six adult trauma ICUs of a level one trauma center in Shiraz, Iran. We also determined the prevalence of DDIs and their associated risk factors. To the best of our knowledge, this is the first study on the effect of various ICU physician staffing models on the incidence and pattern of pDDIs.

Methods

This cross-sectional study was conducted in 6 months (from February to July 2016) in six adult trauma ICUs (nine beds in each ICU, a total of 54 beds) of Shahid Rajaee level one trauma center, Shiraz, Iran. This study was approved by the medical Ethics Committee of the hospital. This center is an educational–therapeutic hospital affiliated to Shiraz University of Medical Sciences.

Standard practice at ICU 1 and 2 (ICU type A) included daily rounds by an attending trauma and neuro-surgeon, once-daily visit by therapeutic intensivist with head nurse and 24 h therapeutic intensivist on-call. In ICU 3 and 4 (ICU type B), an academic intensivist, ICU fellowship, a general physician and head nurse took part in twice-daily rounds. Thus, in ICU type A, an academic intensivist was not always available and was present only as an ICU consultant, while ICU type B took benefit from at least 8 h on-site presence, followed by 16 h on-call presence of an academic intensivist. In ICU 5 and 6 (ICU type C), twice-daily rounds were conducted by a therapeutic intensivist, a general physician and head nurse. Similar to the ICU type B, these ICUs also took benefit from 8 h on-site presence, followed by 16 h on-call presence of a therapeutic intensivist.

Automatic determination of pDDIs was not conducted due to the lack of Computerized Physician Order Entry (CPOE) and no clinical pharmacist was available in these ICUs. Physicians prescribed orders on the patients' files, and then the nurses transcribed them on the administration charts and all the orders were handwritten.

All patients admitted to ICUs, who had received at least two medications with ICU stay for more than 5 days, were included in the study. The patients aged below 18 years old, pregnant women, patients who stayed in ICU for less than 5 days, individuals with incomplete medical records and those who died during their ICU stay were excluded from the study.

A trained pharmacist was responsible for data collection. pDDIs were identified on the first and fifth days after admission in the ICU. The number of pDDIs reported in the results and used in the analyses refers to the sum of pDDIs identified on both first and fifth day.

The patient's information including name, the date of hospital and ICU admission, the date of enrolment in the study, and the name of the physician was collected. Information regarding the patients, physicians, pDDIs, and interventions was dealt with as confidential. The patient's demographic data, such as age, sex, clinical diagnosis, concurrent diseases, medication history, laboratory data, and the history of drug allergy were retrieved from the patient's charts. The prescribed medications, doses, dosage forms, intervals, length of drug use, and route of administration were recorded in a form designed for this purpose. Prescribed drugs were classified according to the Anatomical Therapeutic Chemical Classification codes.[22] The search for pDDIs within prescriptions was conducted through Uptodate[23] and Lexicomp[24] databases, where the DDIs are classified as follows:

A: There are not either pharmacodynamic or pharmacokinetic interactions between the specified drugs.
B: The specified drugs may interact with each other, but there is little to no evidence of clinically significant interaction; no action is required.
C: The specified drugs have a clinically significant interaction with each other, but the benefits of co-administration usually outweigh the risks; the patient should be monitored.
D: There is a strong interaction between the two drugs. Aggressive monitoring is needed, intervention should take place, frequency of use or dosage of drugs should be changed, or, if possible, use alternatives.
X: The risks related to concomitant administration outweigh the benefits; co-administration is considered prohibited or contraindicated.

In this study, pDDIs were defined as interactions belonged to C, D and X categories.[25] For each pDDI, additional information including the drug class, type and mechanism of interaction, clinical consequences, the effects of drugs on each other,

severity, reliability, and proposed clinical management was also provided by the mentioned sources. Note that all studied medication for pDDIs was given concomitantly.

The Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) IV score was also calculated on the day of ICU admission by entering the patient's information in the online APACHE IV score calculator.

Statistical analysis

Statistical analysis was performed using SPSS, the Statistical Package for Social Sciences (SPSS) (version 21 SPSS Inc., Chicago, Ill, USA). The continuous variables were expressed as mean ± SD and the categorical data were presented as the percentage and frequency. Independent *t*-test (if the distribution was normal), and Mann–Whitney *U* (if the distribution was not normal) were used to compare quantitative variables. Chi-square test was conducted to compare sex, as a qualitative variable, between patients with and without type D or X pDDIs. One-way analysis of variance (ANOVA) was exploited to compare APACHE IV scores between ICU types A, B, and C. Kruskal–Wallis test was used to evaluate the possible effect of staffing models on the incidence of pDDIs per patient. Dunn and Tukey tests were used as post-hoc tests of Kruskal–Wallis and ANOVA tests, respectively. Pearson correlation test was used to evaluate the relationship between the rate of pDDIs and each of the quantitative variables such as age, number of drugs, number of orders, and length of ICU stay. Multivariate logistic regression by the enter method was performed to determine the possible association of sex, age, length of ICU stay, type of ICU, number of medications, and orders on the development of either D or X pDDIs. Odds ratio (OR) and their 95% confidence interval (CI) were reported for each variable. For all tests, p-value < 0.05 was considered as the significance level.

Results

During the study period, 288 patients were included in the study, of which 74 cases were excluded due to incomplete information. Of 214 patients, 22 (10.2%) were discharged and went home directly and 178 (83.1%) patients were transferred to other wards. Fourteen (6.5%) patients expired during their ICU stay and were excluded from the study. Finally, the prescriptions of 200 patients (41 in ICU type A, 100 in ICU type B, and 59 in ICU type C) were analyzed. The majority of patients were male (63%) and their mean (SD) age was 41.59 ± 15.16 years. During this 6-month period, 3735 drug orders and 3869 drugs (193 different types) were assessed, of which 68.5%, 20%, and 10.5% of drugs were administered in injectable, oral and both injectable and oral form, respectively. The patients' demographic and clinical data are shown in Table 1. Motor car accident (44%) was the most common cause of admission to ICUs followed by car–car accident (31%), and car turnover (13%).

The mean (SD) of APACHE IV score was 34.22 ± 26.49, 79.62 ± 24.5, and 39.10 ± 25.25 in the ICU types A, B, and C, respectively. The ANOVA test showed that there was a significant difference regarding the APACHE IV score among the three groups ($p = 0.049$). The post-hoc test results demonstrated that the APACHE scores were significantly different between all pairs (p-value = 0.035, p-value = 0.021, and p-value < 0.001 for ICU A *versus* B, ICU B *versus* C, and ICU A *versus* and C, respectively).

A significant relationship was observed between the number of pDDIs and APACHE IV score in ICU type A. Similarly, higher APACHE IV scores were associated with higher numbers of C and D pDDIs (but not X pDDIs) in the ICU type C. In contrast, there was no significant relationship between the number of pDDIs and APACHE IV scores in the ICU type B. In other words, higher APACHE IV scores were not significantly associated with higher frequency of pDDIs in ICU type B. In total, in all the studied ICUs, as the mean of APACHE IV score increased, the number of pDDIs also increased (Table 2).

The most frequent prescribed drugs among the patients were methadone, morphine, acetaminophen, enoxaparin, and potassium chloride (Table 3). Analgesics (11.3%), gastrointestinal drugs (9.4%), and dietary supplements (5.4%) were the most prescribed class of drugs to the patients.

Among the 200 included patients, 1826 potential pDDIs were identified including 1107 (60.6%)

Table 1. Patients' demographic and clinical data.

Quantitative variable	**Range**	**Mean ± SD**			
		ICU A *n* = 41	**ICU B *n* = 100**	**ICU C *n* = 59**	**Total *n* = 200**
Age, years	**18–80**	40.31 ± 13.12	42.35 ± 14.67	41.18 ± 17.34	41.59 ± 15.16
Length of hospital stay (days)	6–90	22.41 ± 19.09	27.63 ± 22.71	24.20 ± 20.49	25.55 ± 21.37
Number of orders per patient	6–44	18.85 ± 10.34	17.45 ± 8.72	20.64 ± 9.98	18.68 ± 9.5
Number of prescribed drugs per patient	9–47	19.07 ± 6.94	18.23 ± 7.42	21.44 ± 8.56	19.35 ± 7.77
Qualitative variable		***n* (%)**			
		ICU A *n* = 41	**ICU B *n* = 100**	**ICU C *n* = 59**	**Total *n* = 200**
Sex	Male	27 (65.8%)	62 (62%)	37 (62.7%)	126 (63%)
	Female	14 (34.2%)	38 (38%)	22 (37.3%)	74 (37%)
History of drug allergy	Penicillin	1 (2.43%)	2 (2%)	0 (0%)	3 (1.5%)
	Aspirin	0 (0%)	0 (0%)	1 (1.69%)	1 (0.5%)
Diagnosis	MCA[1]	23 (56%)	38 (38%)	27 (45.7%)	88 (44%)
	CCA[2]	6 (14.6%)	37 (37%)	20 (33.9%)	63 (31%)
	CT[3]	4 (9.75%)	14 (14%)	7 (11.8%)	25 (13%)
	CPA[4]	7 (17%)	6 (6%)	1 (1.69%)	14 (7%)
	Hanging	0 (0%)	4 (4%)	2 (3.38%)	6 (3%)
	Others[5]	1 (2.43%)	1 (1%)	2 (3.38%)	4 (2%)
The most common drug classes	Cardiovascular system	12 (29.2%)	10 (10%)	9 (15.2%)	31 (15.50%)
	Alimentary tract and metabolism	8 (19.5%)	18 (18%)	5 (8.47%)	31 (15.50%)
	Nervous system	9 (21.95%)	11 (11%)	4 (6.77%)	24 (12%)
	Blood and blood-forming organs	3 (7.3%)	5 (5%)	5 (8.47%)	13 (6.50%)
	Anti-infectives for systemic use	4 (9.75%)	3 (3%)	2 (3.38%)	9 (4.50%)
	Respiratory system	0 (0%)	2 (2%)	1 (1.69%)	3 (1.50%)

[1]Motor car accident.
[2]Car–car accident.
[3]Car turnovers.
[4]Car–pedestrian accident.
[5]Endocarditis, cerebrovascular accidents, unstable angina...

Table 2. The relationship between the incidence of different types of pDDIs and APACHE IV score.

ICU	Type of pDDI	Pearson correlation coefficient (*p*-value)
Type A	C	0.359 (0.021)
	D	0.191 (0.023)
	X	0.298 (0.048)
Type B	C	0.154 (0.125)
	D	0.118 (0.244)
	X	0.0.47 (0.693)
Type C	C	0.121 (0.036)
	D	0.224 (0.048)
	X	0.211 (0.109)
Total	C	0.071 (0.031)
	D	0.009 (0.049)
	X	0.082 (0.024)

ICU, intensive care unit; pDDI, potential drug–drug interaction
ICU type A: Daily visit by therapeutic intensivist and 24 h on-call.
ICU type B: Twice-daily visit by academic intensivist, 8 h attendance in ICU and 16 h on-call.
ICU type C: Twice-daily visit by therapeutic intensivist, 8 h attendance in ICU and 16 h on-call.

type C pDDI, 648 (35.5%) type D pDDI and 71 (3.9%) type X pDDIs. Table 4 demonstrates the frequency of different types of pDDIs in six ICUs. According to Kruskal–Wallis test, there was a significant difference regarding the distribution of pDDIs in three groups of ICUs (all p-values <0.001). The mean of pDDI per patient was higher in the ICU type A than ICU type B and C. There were no significant differences regarding C, D, and X pDDI between ICU1 and 2 ($p=0.103$, 0.291 and 0.281), as well as ICU 3 and 4 (p-value $=0.432$, 0.45, 0.973). Also, there were no significant differences in D and X pDDI between ICU 5 and 6 ($p=0.43$ and 0.86), but the number of C pDDIs was significantly higher in ICU 5 than in ICU6 ($p=0.03$).

In total, 188 (94%), 175 (87.5%), and 49 (24.5%) patients experienced at least one C, D and X pDDI. In ICU type A, 41 (100%), 38 (92.68%), and 17 (41.46%) patients experienced at least one C, D and X pDDI, respectively, while in other types of ICUs these numbers were as follows: 89 (89%), 83 (83%), 12 (12%) in ICU type B and 58 (98.3%), 54 (91.52%), and 20 (33.89%) in ICU type C.

The most common C, D, and X pDDI were found between methadone–morphine (151, 13.6%), spironolactone–KCl (187, 28.8%), and carvedilol–Beta 2 agonists (33, 46.4%). Methadone and KCl (49.1%) comprised most C pDDI, while spironolactone (74.8%) was involved in the largest number of D pDDIs. Table 5 provides the five most common pDDIs in class C, D and X interactions.

Further analysis was conducted to evaluate the correlations between the number of pDDIs and number of prescribed drugs, number of drug orders, age of patients, ICU length of stay and gender (Table 6). The results showed that the mean number of drugs in patients with at least a single C, D, and X pDDI was significantly higher than those without any pDDI ($p<0.001$ for all types of pDDIs; $r=0.551$ for type C, 0.577 for type D, and 0.699 for type X). This was also true regarding the number of orders ($p<0.001$ for all types of pDDIs, $r=0.287$ for type C, $r=0.293$ for type D, and $r=0.671$ for type X) and ICU length of stay ($p=0.047$ and $r<0.05$ for type C; $p=0.002$ and $r<0.1$ for type D or X). Furthermore, patients aged 62 years old or older experienced at least one C, D or X pDDIs more than younger patients ($p<0.001$ and $p<0.003$, respectively).

A total of 113 male and 62 female patients experienced at least one type D pDDI. In addition, among 49 patients with type X pDDI, 32 and 17 were male and female, respectively. The distribution of both type D and type X pDDI between males and females was comparable ($p=0.357$ and $p=0.721$, respectively).

According to multivariate logistic regression analysis (Table 7), type D or X pDDIs were significantly associated with the number of medications (OR = 1.95, 95% CI: 1.68–3.37; $p=0.007$) and ICU length of stay (OR = 1.17, 95% CI: 1.03–2.49; $p=0.034$). In other words, by one additional drug added to the patient's drug regimen and 1 day increase in the ICU stay, there were 1.95 and 1.17 times increase the risk of type D or X pDDIs, respectively. The Hosmer–Lemeshow test p-value was more than 0.05 ($p=0.095$),

Table 3. The most commonly prescribed drugs during the study period and the percentage of patients receiving these medications.

ICU type A		ICU type B		ICU type C		Total	
Drug	***n* (%)**	**Drug**	***n* (%)**	**Drug**	***n* (%)**	**Drug**	***n* (%)**
Methadone	41 (100%)	Methadone	100 (100%)	Methadone	52 (88%)	Methadone	193 (96.5%)
Morphine	40 (97%)	Morphine	98 (98%)	Morphine	48 (81%)	Morphine	186 (93%)
Phenytoin	34 (82%)	Acetaminophen	97 (97%)	Phenytoin	45 (76%)	Acetaminophen	164 (82%)
Magnesium sulfate Pantoprazole, Midazolam Ranitidine Acetaminophen	30 (73%)	Enoxaparin	94 (94%)	Magnesium sulfate	43 (72%)	Enoxaparin	155 (77.5%)
		Propofol	87 (87%)	Pantoprazole, Midazolam	40 (67%)	Potassium chloride	151 (75.5%)
		Potassium chloride	86 (86%)	Ranitidine Acetaminophen	37 (62%)	Phenytoin	150 (75%)
		Ranitidine	73 (73%)			Propofol	143 (71.5%)
Potassium chloride	29 (70%)	Phenytoin	71 (71%)	Potassium chloride	36 (61%)	Ranitidine	140 (70%)
Enoxaparin	26 (63%)	Pantoprazole, Midazolam	68 (68%)	Enoxaparin	35 (60%)	Pantoprazole, Magnesium sulfate, Midazolam	138 (69%)
Propofol	23 (56%)	Magnesium sulfate	65 (65%)	Propofol	33 (55%)	Metoclopramide	123 (61.5%)

ICU, intensive care unit
ICU type A: Daily visit by therapeutic intensivist and 24 h on-call.
ICU type B: Twice-daily visit by academic intensivist, 8 h attendance in ICU and 16 h on-call.
ICU type C: Twice-daily visit by therapeutic intensivist, 8 h attendance in ICU and 16 h on-call.

indicating an appropriate fitness of the model for studied variables. In addition, Cox and Snell R square and Nagelkerke R square indicated that 10.5% and 14.2% of the variances were explained by the model, respectively.

Discussion

This cross-sectional study evaluated the effect of the presence of an academic *versus* therapeutic intensivist and once *versus* twice-daily ICU rounds and hours of presence of intensivist on the incidence of pDDIs, as well as the frequency and related risk factors associated with pDDIs in patients admitted to six trauma ICUs of a teaching–therapeutic level one trauma center. Unfortunately, little attention has been paid to MEs, ADRs and DIs in Iran, and patients' safety is still a neglected area. The study of this theme is even more important in ICUs due to higher risk patients admitted to these wards and the complexity of administered pharmacotherapies.[26] However, few studies have been conducted in this regard in our country.[27–31] Most of the studies in this field have been designed as retrospective cohort studies, without any intervention, and have evaluated the discharged patients' medical records, or have discussed the interaction between only specific drugs.[32–35] To the best of our knowledge, our study is the first study evaluating the effect of intensivist staffing models on the incidence of pDDIs in trauma ICUs.

The majority of the pDDIs including C, D, and X pDDIs occurred in ICU type A (once-daily visit by therapeutic intensivist followed by 24 h on-call) in which the ICU attending was not present. Also, the rate of pDDIs per patient was higher in the ICU C type (twice-daily visit by therapeutic intensivist, 8 h stay in ICU and 16 h on-call), which was

Table 4. The distribution of different types of pDDIs and their relationship with the type of ICU.

Ward		Type C pDDI		Type D pDDI		Type X pDDI		Potential DDIs	
		Total number of C pDDIs	Mean ± SD/ patient	Total number of D pDDIs	Mean ± SD/ patient	Total number of X pDDIs	Mean ± SD/ patient	Total number of pDDIs	Mean ± SD/ patient
ICU type A	ICU 1 ($n=23$)	259 (23.4%)	11.26 ± 6.89	132 (20.37%)	5.7 ± 3.2	22 (30.9%)	0.96 ± 1.1	413 (22.61%)	17.95 ± 7.34
	ICU 2 ($n=18$)	171 (15.4%)	9.5 ± 7.2	89 (13.7%)	4.9 ± 3.5	17 (23.9%)	0.94 ± 1.1	277 (15.16%)	15.38 ± 6.43
	Total ($n=41$)	430 (38.48%)	10.48 ± 7.01	221 (34.1%)	5.39 ± 3.29	39 (54.9%)	0.95 ± 1.09	690 (37.77%)	16.82 ± 6.99
ICU type B	ICU 3 ($n=48$)	159 (14.36)	3.31 ± 2.75	96 (14.8%)	2 ± 1.52	4 (5.6%)	0.08 ± 0.27	259 (14.18%)	5.39 ± 2.52
	ICU 4 ($n=52$)	119 (10.7%)	2.29 ± 1.16	89 (13.7%)	1.71 ± 1.19	8 (11.3%)	0.15 ± 0.36	216 (11.82%)	4.15 ± 2.01
	Total ($n=100$)	278 (25.11%)	2.78 ± 2.13	185 (28.5%)	1.85 ± 1.36	12 (16.9%)	0.12 ± 0.33	475 (26.00%)	4.75 ± 2.34
ICU type C	ICU 5 ($n=31$)	238 (21.5%)	7.67 ± 3.2	137 (21.1%)	4.41 ± 3.4	11 (15.5%)	0.35 ± 0.55	386 (21.13)	12.45 ± 5.94
	ICU6 ($n=28$)	161 (14.5%)	5.78 ± 3.4	105 (16.2%)	3.75 ± 3.1	9 (12.7%)	0.32 ± 0.55	275 (15.06%)	9.82 ± 3.67
	Total ($n=59$)	399 (36.04%)	6.76 ± 3.44	242 (37.3%)	4.1 ± 3.24	20 (28.2%)	0.34 ± 0.54	661 (36.19%)	11.20 ± 5.12
Total		1107 (100%)	5.54 ± 4.9	648 (100%)	3.24 ± 2.89	71 (100%)	0.35 ± 0.16	1826 (100%)	9.13 ± 6.57
p-value	ICU A and B	<0.001		<0.001		<0.001			
	ICU A and C	0.4		0.6		0.2			
	ICU B and C	<0.001		<0.001		0.4			
	Total	<0.001		<0.001		<0.001			

ICU, intensive care unit; pDDI, potential drug–drug interaction
ICU type A: Daily visit by therapeutic intensivist and 24 h on-call.
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ICU type C: Twice-daily visit by therapeutic intensivist, 8 h attendance in ICU and 16 h on-call.

Table 5. The five most common C, D, and X pDDIs.

Risk rating of interaction	Drug pairs	Mechanism of interaction	Observed number (%)
C	Methadone + Morphine	Central nervous system (CNS) Depressants may enhance the CNS depressant effect of Opioid Analgesics.	151 (13.6%)
	Potassium chloride + Enoxaparin	Heparins (Low Molecular Weight) may enhance the hyperkalemic effect of Potassium Salts.	150 (13.5%)
	Potassium Chloride + Heparin	Heparin may enhance the hyperkalemic effect of Potassium Salts.	150 (13.5%)
	Phenytoin + acetaminophen	Fosphenytoin-Phenytoin may decrease the serum concentration of Acetaminophen.	130 (11.7%)
	Spironolactone + Enoxaparin	Heparins (Low Molecular Weight) may enhance the hyperkalemic effect of Potassium-Sparing Diuretics.	122 (11.02%)
D	Spironolactone + Potassium Chloride	Potassium Salts may enhance the hyperkalemic effect of Potassium-Sparing Diuretics.	187 (28.8%)
	Atorvastatin + Diltiazem	Atorvastatin may increase the serum concentration of Diltiazem. Diltiazem may increase the serum concentration of Atorvastatin.	143 (22%)
	Amiodarone + Atorvastatin	Amiodarone may increase the serum concentration of Atorvastatin.	143 (22%)
	Ciprofloxacin + Magnesium sulfate	Magnesium Salts may decrease the serum concentration of Quinolones.	130 (20%)
	Clopidogrel + Fluconazole	CYP2C19 Inhibitors (Strong) may decrease serum concentrations of the active metabolite(s) of Clopidogrel.	40 (6.2%)
X	Carvedilol + Beta 2 receptor agonist	Beta-Blockers (Nonselective) may diminish the bronchodilatory effect of Beta2-Agonists.	33 (46.4%)
	Heparin + Dabigatran	Dabigatran may enhance the anticoagulant effect of Anticoagulants.	21 (29.57%)
	Haloperidol + Metoclopramide	Metoclopramide may enhance the adverse/toxic effect of Antipsychotic Agents.	15 (21.1%)
	Clopidogrel + Sertraline	Agents with Antiplatelet Properties may enhance the antiplatelet effect of other Agents with Antiplatelet Properties.	2 (2.8%)

pDDI, potential drug–drug interaction

a non-teaching ICU and only a therapeutic intensivist was present, in comparison with the ICU type B (twice-daily teaching rounds by academic intensivist, 8 h stay in ICU and 16 h on-call). In a systematic review, ICU physician staffing levels were classified into two groups: 1. High intensity, including mandatory intensivist consultation or closed ICU in which the intensivist is the patient's

Table 6. The relationship between the number of drugs, number of orders, age, and ICU length of stay and the frequency of pDDIs among patients.

Variable	Type of pDDI		Pearson correlation coefficient (*p*-value)
Number of drugs	C	ICU type A	0.560 (<0.001)*
		ICU type B	0.487 (0.061)
		ICU type C	0.026 (0.014)*
		Total	0.551 (<0.001)*
	D	ICU type A	0.502 (<0.001)*
		ICU type B	0.575 (0.057)
		ICU type C	0.259 (0.040)*
		Total	0.577 (<0.001)*
	X	ICU type A	0.856 (<0.001)*
		ICU type B	0.522 (0.081)
		ICU type C	0.750 0.061)
		Total	0.699 (<0.001)*
Number of orders	C	ICU type A	0.612 (<0.001)*
		ICU type B	0.09 (0.361)
		ICU type C	0.117 (0.037)*
		Total	0.287 (<0.001)*
	D	ICU type A	0.388 (0.012)*
		ICU type B	0.236 (0.08)
		ICU type C	0.249 (0.05)*
		Total	0.293 (<0.001)*
	X	ICU type A	0.876 (<0.001)*
		ICU type B	0.543 (0.07)
		ICU type C	0.700 (<0.001)*
		Total	0.671 (<0.001)*
Age	C		0.391 (<0.001)*
	D or X		0.116 (0.032)*
Length of ICU stay	C		<0.05 (0.047)*
	D or X		<0.1 (0.002)*

ICU, intensive care unit; pDDI, potential drug–drug interaction
ICU type A: Daily visit by therapeutic intensivist and 24 h on-call.
ICU type B: Twice-daily visit by academic intensivist, 8 h attendance in ICU and 16 h on-call.
ICU type C: Twice-daily visit by therapeutic intensivist, 8 h attendance in ICU and 16 h on-call.
*Statistically significant

Table 7. The possible association of demographic and clinical characteristics of patients with development of either type D or X pDDIs.

Variable	Odds ratio (95% confidence interval)	*p*-value
Sex	0.532 (0.191–2.17)	0.098
Age	1.84 (0.982–2.81)	0.425
Length of ICU stay	1.17 (1.03–2.49)	0.034
Type of ICU	0.934 (0.164–3.752)	0.462
Number of medications	1.95 (1.368–3.37)	0.007
Number of orders	1.02 (0.672–1.901)	0.998

ICU, intensive care unit; pDDI, potential drug–drug interaction

main attending physician; 2. Low intensity, including elective intensivist consultation or no intensivist. The data analysis showed that hospital and ICU mortality, as well as hospital and ICU length of stay were significantly lower in the high-intensity group.[19] There are several explanations for improved patients' morbidity and mortality, as well as reduced costs of care in intensivists-based ICUs. Intensivists spend most of their working time in ICUs and they have more education, experience and skill in managing life-threatening complications in critically ill patients, and are educated to treat critically ill patients. Moreover, intensivists usually tend to implement the most recent guidelines, protocols and evidence-based medicine to ensure appropriate patient care.[20,36] Another systematic review and meta-analysis of 52 studies showed that high-intensity intensivist staffing was associated with reduced ICU and hospital mortality rate in critically ill patients. However, no further benefits were observed in mortality rate within a high-intensity model by 24 h in-hospital intensivist coverage.[37] Thus, it is obvious from the studies in this area that the multi-professional patient care team is one of the main approaches for patient safety improvement in the ICU.[38] Several studies with conflicting results have compared the "on-demand" and the "24 × 7" models of intensivist staffing in the ICU. In the first model, intensivists deliver critical care to the patients during the day and answer fellows' and residents' questions "on demand" (from home or in-house) during the night. In the second model, an in-house intensivist provides continuous critical care during 24 h a day, 7 days a week. Providing 24 × 7 critical care delivery is associated with improved clinical outcomes, decreased length of stay, enhanced patient and family satisfaction and decreased costs. However, it seems that the 24 × 7 model is mostly efficacious in high-volume, high-acuity ICUs and the benefits of this model cannot be extrapolated to low-volume, low-acuity ICUs.[39]

Our study showed that 94% of patients experienced at least one pDDI during the study period and C pDDI encompassed the majority of identified interactions. In a similar study conducted in the ICU of a Brazilian teaching hospital in a 12-month period in 2015, at least one pDDI was identified in 89% of prescriptions and the majority of pDDIs were moderate. In their study, the Micromedex database was used to search for pDDIs in prescriptions and pDDIs were classified into four categories: contraindicated, major, moderate, and minor. Also, the frequency of usage of prescribed drugs was continuously monitored by the FAST HUG (Feeding; Analgesia; Sedation; Thromboembolic prophylaxis; Head-of-bed elevation; stress Ulcer prophylaxis; and Glycaemic control) strategy in this study.[40]

Vanham and her colleagues investigated the prevalence and patterns of pDDIs in two German academic ICUs, using three resources including Stockley's, Micromedex, and Epocrates. Some 79% of patients had at least one pDDI, and major pDDIs were identified in 18% of patients. In our study, C pDDIs (considered as major interactions) occurred in at least 94% of patients. Similar to our study, clinical pharmacists were not involved in ICUs and no pharmacist was checked for pDDIs. On the other hand, in contrast to our study, a CPOE system was used by ICU physicians to prescribe drugs and document their orders. This study showed that the reliability for identifying pDDIs between different resources was poor, and also discrepancies existed between the judgment of intensivists. Thus, lack of fully comprehensive and relevant information in this area is greatly felt. Furthermore, in this study potential adverse reactions of contraindicated and major pDDIs were evaluated and it was observed that 4% of patients experienced related ADEs.[41]

Our results demonstrated that analgesics were the most common prescribed drugs, and also the

most frequent life-threatening pDDIs (X and D) belonged to this drug class. DDIs involving opioids can lead to acute exacerbations of pain, or withdrawal symptoms.[42] This result was expected because this study was conducted in adult trauma ICUs and the majority of patients received analgesics for pain relief. Thus, the types of drugs involved in the pDDIs are closely dependent on the ward in which the study has taken place. For example, in one study conducted at the cardiothoracic ICU of a teaching hospital in Iran, antibiotics, central nervous system agents and cardiovascular drugs were the three most commonly prescribed and interacting drug classes.[43]

Data analysis revealed that there was a significant relationship between the incidence of pDDIs and the number of drugs, number of orders, ICU length of stay, APACHE score and age of the patients, while sex did not have any significant impact on the rate of pDDIs. Some previous studies showed a significant relationship between sex and prevalence of pDDIs. Gagne *et al.*,[44] Moura *et al.*,[45] and Rafieii *et al.*[31] in separate studies concluded that men were at higher risk of pDDIs as compared with women, while Cremades *et al.* demonstrated that pDDIs were more common in women than in men.[46]

Logistic regression analysis showed that the number of medications and ICU length of stay were the only attributable risk factors for the incidence of D and X pDDIs. Our results were consistent with Namazi *et al.*'s study which was conducted in neurological wards of two teaching hospitals in Shiraz.[47] In general, the higher the number of medications, the greater the risk of ADEs and pDDIs.[14]All patients received more than nine drugs in our study. Drug regimens complicated by the high number of medications were considered as a modifiable risk factor for ADEs. Thus, it is suggested that drug regimens should be monitored regularly in patients admitted to ICUs in order to discontinue drugs when unnecessary, such as drugs administered as prophylactic agents. Pharmacists can have crucial roles in medical teams using this type of monitoring.[48] In our study, prolonged ICU length of stay was associated with higher incidence of pDDIs, probably through an indirect effect. In other words, an increase in the hospitalization period will lead to an increased number of prescribed drugs. Janković *et al.* showed that each additional day of stay in ICU increased the number of pDDIs for about 0.1.[49] In our study, the patients who had higher APACHE IV scores were at greater risk for pDDIs. Our results are consistent with those of Sierra *et al.*'s study in which a significant relationship was observed between the number of pDDIs and APACHE score.[50]

The software used in the current study was Lexicomp. This software has some advantages and disadvantages. It can determine the severity and reliability of the DDIs and it presents some suggestions on the management of the DDI and drug-dose adjustment. However, it lacks proper timing of drug administration. Vonbach *et al.* evaluated nine DDI resources, of which Drug Interaction Facts, Drug-Reax, Lexi-Interact and Pharmavista were considered superior in comparison to others. The results showed that Drug Interaction Facts was the least qualified program due to containing the smallest number of drugs. In Lexi-Interact, excessive condensation of individual drugs into drug classes was done resulting in less specific information; however, it showed the best sensitivity. Finally, the authors concluded that Pharmavista and Drug-Reax contained excellent DDI monographs.[51]

Our study has some limitations. First, this study was conducted in a single hospital. This issue had a negative effect on the generalization aspect of the results. Second, we were not aware of the physician's reason to prescribe two drugs with potential interaction. It is possible that the benefit of their co-administration outweighs the risks. Third, only one DDI database was utilized in this study, while some DDIs are only identified through other resources except for Lexicomp. Fourth, the ADEs and clinical outcomes of the patients related to pDDIs were not evaluated because patient follow-up was not possible in this study. Thus, further multicenter studies evaluating DDIs in patients admitted to trauma ICUs using various DDI databases as well as monitoring patients for probable ADEs are required.

Conclusion

Our study showed that the rate of pDDIs was high in adult trauma ICUs and the majority of patients experienced at least one pDDI during their ICU stay. PDDIs were significantly lower in teaching ICUs with the presence of ICU attending in comparison with non-teaching and also consult-based intensivist ICUs. The findings

provide evidence that the twice-daily visit and 8 h attendance by 16 h on-call academic intensivist is superior in reducing pDDIs in comparison with therapeutic intensivist with simultaneous schedule, and also therapeutic intensivist once-daily visit and 24 h on-call, respectively.

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Conflict of interest statement

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