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CHEMICAL INCOMPATIBILITIES OF I.V ADMIXTURE COMBINATIONS IN ICU, ORTHOPEDIC AND EMERGENCY UNITS OF VARIOUS HOSPITALS AND MEDICAL CENTERS IN SANA'A, YEMEN

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ABSTRACT

Background: Intravenous incompatibilities are unwanted reactions that occur when two or more drugs are administered through the same intravenous line or in the same solution. They can cause toxicity in the patient or a lack of therapeutic effect. **Aims:** The aim of this study was to investigate the chemical incompatibilities of IV admixture combinations in Sana'a's public and private hospitals. **Methods:** A cross-sectional, prospective, and quantitative study was conducted from December 2020 to July 2021. Data was collected from medical files of patients admitted to ICU, orthopedic and emergency department of public and private hospitals in Sana'a City, Yemen. Chemical drug incompatibilities were identified based on the analysis of the patient prescriptions using a PH measurement meter. **Results:** A total of 900 prescriptions were screened, and 100 drug combinations met the criteria for inclusion. The average number of prescribed drugs was 7 ± 4 drugs per prescription. Of these, 53% were prescribed with four or more IV drug mixtures that were analyzed at zero, one, two, and three hours. The proportion of IV admixtures contained four drugs (38%), 5 drugs (29%), 6 drugs (17%), 7 drugs (12%), 8 drugs (2%), and 9 drugs (2%). Further, Vitamin C (9.8%), Vitamin B complex (B1,B2,B3,B5,B6,B12,Biotin and folic acid (9.1%)), and Pantoprazole sodium (7.16%) were the most commonly prescribed drugs. Approximately 97 % of prescriptions had at least one potential chemical incompatibility. The most chemical incompatibilities were found in 9 IV admixtures (D.N. S+ Vit.B complex +Vancomycin + Kcl + Rabeprazole +Vit.C +Tramadol +Ceftriaxone +Dexamethasone +Furosemide), followed by 7 IV admixtures (DNS +Vit B complex +Ondansetron HCL dihydrate +KCL +Hydrocortisone +Vit), and 6 IV admixtures (N/S +Heparin + ceftriaxone +N-acetyl cysteine + Citicoline +Furosemide +Pantoprazole). **Conclusion:** The findings of this study suggest that the majority of IV drug admixtures indicated chemical incompatibility. The findings of this study provide the basis for drug-infusion compatibility and aid in avoiding intravenous drug incompatibilities by demonstrating that drugs with similar pH will be compatible with IV combinations.

KEYWORDS: intravenous drug incompatibilities, chemical incompatibilities, pH, drug-infusion compatibility.

1. INTRODUCTION

Bloodstream Intravenous combinations are the preparation of a pharmaceutical combination of two or more medications into a huge bag of Intravenous fluids, primarily Normal Saline Solution (0.9 % NaCl) or Dextrose (5 %), under the medical supervision, nurse practitioners, and qualified pharmacists.[1] It is widely used for a variety of reasons, including its rapid onset, high bioavailability, and rapid clearance, making it perfect for dose adjustment and effect maintenance. The number of IV drugs given to these patients is frequently higher than the number of peripheral intravenous lumens. As a result, co-administration of many drugs in the same infusion is completely avoidable.[1]

A greater number of medications increase the risk of incompatibility geometrically. Health professionals, on the other hand, have a poor understanding of this complex situation. In modern medicine, up to 80% of hospitalized patients receive intravenous therapy at the same time at their admission. Medication, fluids, nutrition, and blood products can all be given intravenously (peripheral or central). However, these practices are not common without risks, which include

mortality and morbidity, increased hospital stay, and significant costs.[2]

There are two types of drug incompatibilities: chemical and physical. The chemical reactions occur when more than 10% of the molecular alteration is degraded, with hydrolysis being the most common reaction.[3] The temperature and pH of the drug solution are related to this type of reaction.[3,4] Physical incompatibilities, on the other hand, are manifested by changes in colour and viscosity; precipitation; turbidity of the solution; or gas release.[3,4,5] These reactions can occur immediately or later, and are estimated to occur in 3% to 25% of treatments administered[4], accounting for 60% of serious problems and adverse events in hospitals.[6] The primary method of drug delivery in emergency, orthopaedic and intensive care units (ICUs) is intravenous route, which gives maximum safeness and an instant therapeutic influence in the bloodstream.[7]

Other chemical incompatibilities include the reaction of two or more substances, which results in a change in the chemical properties of a pharmaceutical dosage form. This can result in the formation of a toxic or inactive product.[8] Chemical incompatibilities occur as a result of drug and additive chemical properties such as pH change: oxidation-reduction reactions, acid-base hydrolysis double decomposition, and complex formation.[9]

Hospitalized patients admitted to emergency or orthopaedic or ICU departments are considered a major category for drug incompatibilities since they frequently necessitate the need for multiple medications, the majority of which are injected intravenously. The relatively small number of peripheral vascular access routes among such individuals is a significant issue, decrease the safe use and handling of IV injections that should hopefully have a various access routing path for each medication. Most injections in these circumstances take place via a Y-site plug, through which medicine are prepared individually but combined in the cannula lumen before entering the bloodstream. Because chemical changes necessitate longer time to follow - up for substantial declines in therapeutic concentrations to take place, the medicine must be physiologically consistent to be administered concurrently.[10]

In Yemen which is a developing country with a poor healthcare system, and absence of any comprehensive regulations controlling drug- drug interactions, there is very little information available regarding the IV incompatibilities. This can sometimes lead to severe adverse drug reactions in patients.[11] It is not possible to predict all incompatibilities that may arise, but the presence or alertness of a clinical pharmacist in the ward rounds, clinical review about the possible incompatibilities, and making nurses aware of the incompatibility problems will significantly improve patient safety.[12]

In general, there is still a scarcity of published data on intravenous medication and there is insufficient information about IV drug incompatibilities to compile evidence for identifying the best recommendations for mitigating the potential risks associated with the drug safety process in Yemen. Identifying these issues and questions, as well as developing solutions, has resulted in the research objectives. The overall goal of this study is to identify potential chemical incompatibility in some Yemeni hospitals, to improve the quality of nursing care, and close the gaps between theoretical precepts and daily clinical practice.

2. MATERIAL AND METHOD

2.1. Study design and setting

This was a cross-sectional prospective descriptive study and data was collected from patients admitted to ICU, orthopaedic and emergency departments of public and private hospitals in Sana'a, the capital of Yemen. Public hospitals include Al-Thawra Hospital, Al-Sabeen Hospital, and Al-Kwaite Hospital. Whereas, private hospitals include Azal Hospital, Al-motawakel Hospital, Uni-Max Hospital, Al-Majd Hospital, Al-Haramine Hospital and Science and Technology Hospital.

Data was collected in the period between December 2020 and July 2021. Inclusion criteria included patients receiving medical prescriptions with co-infusion not less than 4 IV drugs. . Only one prescription per patient was analysed. While the exclusion criteria stipulated that patients receive a continuous intravenous infusion but no Y-site drug administration. Cases in which the drugs were prescribed for use only when necessary, patients under 18 years of age, and drugs that were unavailable in the database to assess their incompatibilities were excluded.

2.2 Data Collection

Clinical data was collected prospectively and physically from medical files of the targeted patients and analysed. The compatibility of the selected critical care drugs when administered as continuous intravenous infusions was determined using UCL Hospitals Injectable Medicines (2013) and Newton, D. W. (2009) and then tested chemically. When a single drug is administered via infusion, three trained and medical experts (clinical pharmacists) examined the drug's compatibility in the infusion solution. In addition, and when two or more drugs were used in the same infusion line then drug-drug compatibilities were also checked. For each prescription, the specific types of data required to measure chemical compatibility status were recorded and directly entered into the prepared compatibility checklist form. Drug-drug compatibility is also checked when four or more drugs are used in the same infusion line.

2.3. Sample Size

The following parameters were used to calculate sample size: 50% (potential incompatibility (PI) occurrence, 7% absolute accuracy, plus 10% to contribute for expected losses). The significance level was set to 5%. Data was retrieved from 900 prescription medicines and analyzed by using the Statistical Package for the Social Sciences (SPSS) software version 23.0 . As necessary, descriptive analysis of the results was performed. Continuous variables were analysed using the descriptive statistics (mean, standard deviation (SD).

3. RESULTS

A total of 900 prescription drugs were identified. Of these prescriptions, 100 prescriptions which have more than 4 drugs in each prescription met the inclusion criteria and were analysed. The number of IV admixtures ranged between 4 to 9 drugs per prescription. Table 1 depicts that Vitamin C 49 % (49/100) was the most common prescribing medication followed by Vitamin B complex (B1, B2,B3, B5,B6,B12,Biotin and folic acid) 47% (47/100) and promethazine hydrochloride, amikacin, and atropine sulphate were the least prescribing drugs (1%) (1/100).

Table 1: Details of frequency of IV Admixtures.

No	Name of drug	Frequency	Percentage
1	Vitamin C (ascorbic acid)	49	9.8%
2	Vitamin B complex (B1, B2, B3, B5,B6,B12,Biotin and folic acid)	47	9.1%
3	Pantoprazole sodium	37	7.16%
4	Ceftriaxone sodium	33	6.38%
5	Tramadol hydrochloride	30	5.80%
6	Furosemide sodium	30	5.80%
7	Metoclopramide hydrochloride	27	5.22%
8	Dexamethasone sodium phosphate	22	4.26%
9	N-acetylcysteine sodium	18	3.48%
10	KCL	17	3.29%
11	Omeprazole Magnesium	17	3.29%
12	Vancomycin hydrochloride	15	2.90%
13	Meropenem sodium	14	2.71%
14	Ca gluconate	13	2.51%
15	Tranexamic acid	12	2.32%
16	Diclofenac sodium	12	2.32%
17	Ondansetron hydrochloride	11	2.13%
18	Imipenem +Cilastatin sodium	11	2.13%
19	Phenytoin sodium	11	2.13%
20	Hydrocortisone sodium succinate	10	1.93%
21	Cefepime hydrochloride	8	1.55%
22	Heparin sodium	8	1.55%
23	Turosemide sodium and chloride	4	0. 8%
24	Ranitidine hydrochloride	4	0. 8%
25	Vitamin K (phytonadione)	4	0. 8%
26	Piracetam	4	0. 8%
27	Oxytocin acetate hydrate	4	0. 8%
28	Amoxicillin + clavulanic acid sodium	4	0. 8%
29	Esomeprazole Magnesium	3	0.58%
30	Tazobactam +piperacillin sodium	3	0.58%
31	Amoxicillin sodium	3	0.58%
32	Rabeprazole sodium	3	0.58%
33	Gentamycin sulphate salt	2	0.39%
34	Dopamine hydrochloride	2	0.39%
35	Ampicillin+ Cloxacillin sodium	2	0.39%
36	Ceftazidime sodium	2	0.39%
37	Citicoline sodium	2	0.39%
38	Drotaverine hydrochloride	2	0.39%
39	Clindamycin hydrochloride hydrate	2	0.39%
40	Cerebrolysin	2	0.39%
41	Promethazine hydrochloride	1	0.2%

42	Acyclovir sodium	1	0.2%
43	Neostigmine bromide	1	0.2%
44	Nor adrenalin bitartrate monohydrate	1	0.2%
45	Mg sulfate	1	0.2%
46	Paracetamol	1	0.2%
47	Hyoscine-N- butylbromide	1	0.2%
48	Amikacin	1	0.2%
49	Labetolol	1	0.2%
50	Chlorophenaramine	1	0.2%
51	Enoxaparine sodium	1	0.2%
52	Dobutamine hydrochloride	1	0.2%
53	Atropine sulfate	1	0.2%
		∑f = 517	100%

Table 2 indicated the percentage of acidic and basic drugs prescribed in IV admixtures. The majority of the drugs were acidic 34% (34/100) and others were basic drugs 19% (19/100). Most drugs, such as aminophylline sod, esomeprazole sod, omeprazole sod, Pantoprazole, phenytoin sod, and Torsemide, have a basic pH (> 7) or a high pKa and will theoretically precipitate in low pH solutions such as 5% glucose (pH 4-4.5) and DNS (pH 3.2).

Table 2: Details on pH of IV Admixtures.

Acidic Drugs	pH	Basic Drugs	pH
N-Acetcysteine	6-7.5	Ampicillin+cloxacillin	8
Amikacin	3.5-5.5	Amoxicillin	8-10
Ampicillin+ cloxacillin	6.5	Amoxicillin + clavulanic acid sodium	8-10
Atropine	4.5-6.5	Acyclovir	11
Cefepime	4-6	Ca gluconate	6-8.2
Ceftriaxone	6.7	Cerebrolysin	6.8-8
Ceftazidime	5-8	Cilastatin +imipenem	6.5-8.5
Clindamycin	3.4	Citicoline	7.2
Chlorpheniramine	4-5.2	Diclofenac	8.25
Dobutamine	2.5-5.5	Dexamethasone	7-8.5
Dopamine	3.3	Esomeprazole	9-10
Drotaverine	3.8	Furosemide	8-9.3
Enoxaparine Na	5.5-7.5	Meropenem	7.5-8.5
Heparin	5-8	Mg sulfate	10.5
Hydrocortisone	5-7	Omeprazole	11

Table (3) shows the percentage of IV admixtures containing four drugs (38 %), five drugs (29 %), six drugs (17 %), seven drugs (12 %), eight drugs (2 %), and nine drugs found in this study's 100 IV admixtures (2 %)

Table 3: Details of frequency of 4 or more IV Admixtures.

Number of drugs	Frequency (%)
4 drugs	38 (38%)
5 drugs	29 (29%)
6 drugs	17 (17%)
7 drugs	12 (12%)
8 drugs	2 (2%)
9 drugs	2 (2%)

3.1 Chemical Incompatibility

Table 4 depicts medical prescriptions which contain 4 or more IV admixtures and the incompatibility was identified based on identified based on UCL Hospitals Injectable Medicines[13], and Newton, D. W.[5] As shown in table 4, IV drugs combinations more than 9 e.g D.N. S+Vit.B complex + Vancomycin + Kcl + Rabeprazole + Vit.C +Tramadol+ Ceftriaxone +Dexamethasone +Furosemide, were incompatible. The reason was based on (UCL Hospitals Injectable Medicines, 2013; Newton, D. W. 2009) that recommended avoid infusion Tramadol with any medications. Other data were prescribed in details in table 4.

Table 4: Details on frequency of usage of Incompatible IV Admixtures.

Iv Admixtures drugs	N	pH diff	Chemical compatibility (UCL Hospitals Injectable Medicine[13] & Newton, D.W.[5]
DNS+Vit.B complex +Vancomycin +Kcl + Rabeprazole + Vit.C + Tramadol + Ceftriaxone + Dexamethasone + Furosemide	9	1.6	Incompatible **Reason :** Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Dexamethasone +Furosemide
N/S + vitamin B complex +metoclopramide +vitamin C +tramadol +ceftriaxone +cerebrolysin +citicoline +furosemide +pantoprazole	9	1.65	Incompatible **Reason :** Don't infuse Tramadol injection with any other medicines Ascorbic acid and ceftriaxone sodium are incompatible
DNS + Vitamin B Complex + Ondansetron HCL Dehydrate + KCL + Hydrocortisone + Vitamin C + Ceftriaxone + Furosemide + Omeprazole	7	3.76	Incompatible **Reason :** Do not infuse omeprazole injection with any other medicines ascorbic acid and ceftriaxone sodium are incompatible All the drugs in the infusion are acidic except Furosemide and Omeprazole
Piracetam + N-Acetyl cysteine + furosemide + Amoxicillin clavulanic acid + pantoprazole	7	3.78	Incompatible **Reason :** All drugs in the infusion were acidic except furosemide, Amoxicillin, and pantoprazole
Dextrose + vitamin B complex + metoclopramide + vitamin C + tramadol + ceftriaxone + diclofenac sodium + omeprazole	7	3.66	Incompatible Do not infuse Diclofenac sod injection with any other medicines. Do not infuse omeprazole injection with any other medicines Ascorbic acid and ceftriaxone sodium are incompatible Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Diclofenac Na, and omeprazole
N/S+ Vit B+ Kcl+ Drotaverine+ Vit C+ Piracetam+ N-ace cysteine + Furosemide	7	0.9	Incompatible **Reason** : All the drugs in the infusion are acidic except Furosemide
N/S+ Vit.B +Vancomycin +Vit.C +KCL +Ca gluconate +Pantoprazole	6	2.1	Incompatible **Reason** : All the drugs in the infusion are acidic except Ca gluconate, and Pantoprazole
N/S+ Vit B complex +metoclopramide +Heparin + Vit C +Tramadol+omeprazole	6	2.58	Incompatible **Reason :** Do not infuse omeprazole injection with any other medicines Don't infuse Tramadol injection with any other medicines. All the drugs in the infusion are acidic except omeprazole
N/S + Heparin +hydrocortisone +Vit C + Vit B complex + (Imipenem + Cilastatin) + omeprazole + phenytoin + Ca gluconate)	7	1.3	Incompatible **Reason** : Do not infuse omeprazole injection with any other medicines
N/S+ Vit B +Metoclopramide +Heparin +vit C +Tramadol +Ceftriaxone +Diclofenac Na	7	0.53	Incompatible **Reason** : Do not infuse Diclofenac sod injection with any other medicines Ascorbic acid and ceftriaxone sodium are incompatible Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Diclofenac Na
R. L+ Vit B + Vit C Metoclopramide+ Ceftriaxone+ Tramadol + Diclofenac Na + tranexamic acid	7	1.06	Incompatible **Reason** Do not infuse Diclofenac sod injection or tramadol injection with any other medicines Do not infuse Tranexamic acid with any other medicines, ascorbic acid and ceftriaxone sodium are All the drugs in the infusion are acidic except Diclofenac Na, and

			tranexamic acid
Vitamin B +Metoclopramide +Vitamin C +Tramadol +Tranexamic Acid +Dexamethasone +Diclofenac Na	7	0.77	Incompatible **Reason** Do not infuse Diclofenac sod or Tramadol injection with any other medicines Do not infuse Tranexamic acid with any other medicines
N/S + Vit B complex + oxytocin + Heparin +vit C + Diclofenac Na +Ceftriaxone+ Tramadol	7	1.5	Incompatible **Reason** Do not infuse Diclofenac sod injection or tramadol injection with any other medicines. Ascorbic acid and ceftriaxone sodium are incompatible
N/S + Vit. B +Metoclopramide +Heparin +Vit.C +Tramadol +Ca gluconate +Pantoprazole	7	2.24	Incompatible Reason Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Ca gluconate and pantoprazole
Dextrose+ Vitamin B + Vancomycin + Vitamin C + Tramadol +Ca gluconate + Imipenem +Omeprazole	7	2.77	Incompatible **Reason** Don't infuse Tramadol injection with any other medicines Do not infuse omeprazole injection with any other medicines
N/S +Vit B+ Vancomycin +Vit C +Ondansetron +N-acetyl cysteine + Meropenem +Pantoprazole	7	1.3	Incompatible **Reason** All the drugs in the infusion are acidic except Meropenem and pantoprazole
D.N.S +Vit B + KCl + Linezolid + Vit C+ Ca gluconate +Imipenem + Torsemide	7	3.49	Incompatible **Reason** All the drugs in the infusion are acidic except Ca gluconate, Imipenem, and Torsemide
N/S +Metoclopramide +Hydrocortisone +Tramadole +Tranexamic acid +Pantoprazole	6	2.73	Incompatible **Reason** Do not infuse Tranexamic acid with any other medicines, Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Tranexamic acid, Pantoprazole
N/S +Vit B + Cefepime +Vit C+ N- acetcysteine + furosemide +pantoprazole	6	1.52	Incompatible **Reason** All the drugs in the infusion are acidic except furosemide + Pantoprazole
N/S +Vit B + Dopamine+Cefepime +Vit C +N-acetcysteine + Dexamethasone	6	1.4	Incompatible **Reason** All the drugs in the infusion are acidic except Dexamethasone
D.N.S +Vit B + Vancomycin + Vit C +Furosemide +Omeprazole	6	1.31	Incompatible **Reason** Do not infuse omeprazole injection with any other medicines All the drugs in the infusion are acidic except Furosemide and Omeprazole
D.N. S+Vit B Vit C +Ceftriaxone + Dexamethasone+ (ampicillin +cloxacillin) +Diclofenac Na	6	4.13	Incompatible **Reason** Do not infuse Diclofenac Na injection with any other medicines Ascorbic acid and ceftriaxone sodium are incompatible
D.N.S + vit Bvit C +metoclopramide +Ceftriaxone +Tramadole +Diclofenac Na	6	1.42	Incompatible **Reason** Do not infuse Diclofenac sod injection with any other medicines Ascorbic acid and ceftriaxone sodium are incompatible Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Diclofenac Na
Dextrose+ noradrenaline +dopamine + ceftriaxone	6	5	Incompatible

+Ca gluconate + (amoxicillin + clavulanic acid) + pantoprazole			**Reason** Three drug are acidic and three are basic
D.N. S+ Metoclorbromide +Oxytocin +Ceftriaxone +Tramadol+ Ranitidine +Diclofenac Na	6	2.25	Incompatible **Reason** Do not infuse Diclofenac sod injection with any other medicines Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Ranitidine , and Diclofenac Na
D.N.S + Metoclorbromide +Oxytocin +Hydrocortisone +Ceftriaxone +Tramadol +Diclofenac Na	6	2.93	Incompatible **Reason** Do not infuse Diclofenac sod injection with any other medicines Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Diclofenac Na
N/S + metoclopramide + Kcl + ceftazidime + Tramadole+ Dexamethasone + phenytoin + omeprazole	6	3.24	Incompatible **Reason** Don't infuse Tramadol injection with any other medicines Do not infuse omeprazole injection with any other medicines All the drugs in the infusion are acidic except Dexamethasone, phenytoin , and omeprazole
N/S +vit B + KCl +Vit C+Meropenem +pantoprazole +phenytoin	6	2.75	Incompatible **Reason** Three drug are acidic and three are basic
N/S + Vit B + vancomycin + ondansetron + Vit C+ Meropenem+ pantoprazole	6	4.5	incompatible All the drugs in the infusion are acidic except Meropenem+ pantoprazole
N/S +Vit B +Vit C +Hydrocortisone+ dexamethasone +Furosemide	6	1.12	Incompatible **Reason** All the drugs in the infusion are acidic except dexamethasone and Furosemide
N/S +KCL Enoxaparine Na +Dexamethasone +Meropenem +Furosemide +Omeprazole	6	3	Incompatible **Reason** Do not infuse omeprazole injection with any other medicines All the drugs in the infusion are basic except KCL and Enoxaparine Na
N/S +vancomycin +KCl + Tramadol+ Ca gluconate +Imipenem +Omeprazole	6	2.7	Incompatible **Reason** Do not infuse omeprazole injection with any other medicines Don't infuse Tramadol injection with any other medicines
D.N.S Vit B +Metoclopramide +KCl +Vit C+ Tramadol + Pantoprazole	6	2.11	Incompatible **Reason** Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Pantoprazole
Glucose +Vit B +Metoclopramide + Paracetamol amp +Vit C +Dexamethasone +Diclofenac Na	6	1.75	Incompatible **Reason** Do not infuse Diclofenac sod injection with any other medicines All the drugs in the infusion are acidic except Dexamethasone and Diclofenac
D.N. S+ Vit B+ Amino acid + Vit C+ Ca gluconate+ Turosemide	6	3.55	Incompatible **Reason** All the drugs in the infusion are acidic except Ca gluconate and Turosemide
D/W +Vit k + Transamic acid +furosemide + (Amoxicillin+ clavulanic a) + esomeprazole	5	3.6	Incompatible **Reason** Do not infuse Tranexamic acid with any other medicines All the drugs in the infusion are basic except Vit k
D.N. S + Ondansetron + Ca gluconate +Meropenem +Frusemide + Esomeprazole	5	0.8	Incompatible **Reason**

			All the drugs in the infusion are basic except Ondansetron
D.N.S + Vit.B complex + Metoclopramide +Vit.C +Tramadol +Dexamethasone	5	1.46	Incompatible **Reason** Don't infuse Tramadol injection with any other medicines All the drugs in the infusion are acidic except Dexamethasone
D.N. S+ hydrocortisone + Vit C Ceftriaxone +Furosemide +Omeprazole	5	2.54	Incompatible **Reason** Do not infuse omeprazole injection with any other medicines

4. DISCUSSION

Administration of multiple IV drugs is considered a major issue due to the possibility of inducing incompatibility. The current research focused on the identification of chemical incompatibility of IV drug combinations administered to ICU, orthopaedic, and emergency patients.

In this study, we found that 97% of the total IV drug admixture was chemically incompatible. This finding is higher than two previous studies conducted in Brazil by Marsilio, N. R et al[3] and in Spain by Moaes et al.[14] which both revealed that majority of ICU prescriptions were incompatible. The high number of prescriptions with incompatibilities identified in this unit could be attributed to the large number of drugs prescribed to critically ill patients, which is necessary given the complexity of their clinical conditions. Drug interactions become more common as the number of drugs prescribed increases exponentially.

Our results also indicated that the number of IV admixture drugs were 38% among patients who receive four drugs, 29% for patients who receive five drugs, and 17% for patients who receive six drugs. This finding was higher than the findings of Vogel Kahmann et al[15] who analysed 78 different drugs and found that 15% of the combinations tested exhibited drug incompatibility reactions, and Marsilio, N. R et al[3] who analysed 100 prescriptions and reported incompatibilities of 14.6%. The discrepancies might explain these differences in prevalence include the diversity of morbidity profiles among the samples that might change the drug therapy profile to be used and, consequently, the frequency of drug incompatibilities

Our data also revealed that Vitamin C and Vitamin B complex were the most commonly prescribed drugs involved in IV admixture incompatibilities. This finding contradicted the findings of Marsilio, N. R et al[3], who reported that the most common incompatible drugs were midazolam, hydrocortisone, and vancomycin. The high frequency of these drugs in incompatibilities may be relative because they are commonly used in critical care units and thus appear in a large number of prescriptions. Furthermore, vitamin C and multivitamins are widely used intravenously in Yemeni public and private hospitals to prevent oxidative stress and to assist the body in healing skin wounds, cuts, and scrapes faster. Furthermore, the majority of prescriptions came from patients who had been injured as a result of Yemen's civil war, which may explain the high frequency of MV among infusions in this setting.

In this study, majority of patients who prescribed with vitamins, anti-ulcer, anti-inflammatory, and antibiotics showed chemical incompatibility. Antibiotics and supportive medications (e.g., anti-inflammatory, anti-epileptic, antiulcer, and diuretics) were frequently administered via the same route, which could explain the incompatibility with these infusions (infusions–injections). Further, most groups with basic pH e.g phenytoin, Diclofenac sod, Esomeprazole, Furosemide, Pantoprazole sod, Torsemide, and Calcium gluconate were chemically incompatible. Phenytoin solution is a basic drug (pKa=8.3) and it has very poor aqueous solubility. It is easily precipitated when combined with DNS or acidic drug solute combinations. When Phenytoin infused with a 5% glucose solution, precipitation occurred within 10 – 15 minutes.[15] This precipitation is affected by the solubility, thus, the amount of precipitation is determined by the initial pH of the phenytoin solution as well as the pH of the solution for reconstitution.[15]

In our study, the most common drugs incompatibilities were found among a combination of (D.N.S + Vit.B complex + Vancomycin + Kcl + Rabeprazole +Vit.C +Tramadol+ Ceftriaxone +Dexamethasone +Furosemide). Based on recommendation by UCL Hospitals Injectable Medicines,[13] and Newton, D. W.[5], infusion of Tramadol injection with any other medicines or mixing acidic and basic drugs may result in chemical incompatibilities.

In our data, we reported incompatibility of infusion of diclofenac Na with other medications such as Glucose, Vit B, Metoclopramide, Paracetamol amp, Vit C, and dexamethasone injections). Based on a recent conclusion of one study conducted by Leuratti, C et al[16] and his colleges, the tolerability of diclofenanc sodium at 75 mg/1 mL solution administered as a 5-s i.v. bolus was safe when administered alone. Further, a recent case study done in Jordan by Naser, A. Y,[17] and his colleagues reported that combination between diclofenac and dexamethasone mixture resulted in a death of 3 patients suffering from cardiovascular diseases in 24 hours of receiving dexamethasone and diclofenac injection mixture. Their study suggested that mixing

them together in the same syringe maybe associated with increased risk of death.

Our findings also revealed a chemical incompatibility between IV infusions of Tramadol with metoclopramide administration. Similar observations were obtained in another research, where infusion of these medications accounted for 60% of drug incompatibility.[18] According to the Drugs.com database, an infusion of tramadol and metoclopramide is extremely harmful and, depending on the duration of treatment and the dose, may result in the life - threatening illness.[19]

Our findings also showed a chemical incompatibility between Omeprazole and phenytoin infusion, which potentially increasing serum concentrations of phenytoin and hence its toxic effects such as suppressing liver metabolism and decrease its excretion. In addition to lab monitoring for phenytoin adverse effects, mixing between these prescribed medications necessitates the assessment of clinical manifestations of toxic effects, such as sleep deprivation, vision problems, modifications in metal status, convulsions, stomach cramps, and muscle weakness.[19]

Overall**,** combinations of intravenous infusion dosage forms are typically not suggested because of the possibility for incompatibilities and subsequent loss of activity of one or both prescribing medications. Regrettably, there may be significant evidence to mix two or more parenteral administration drugs in the same infusion, syringe, or at a Y-site junction where two or more IV met the requirements in some cases.

4.1 Limitations and recommendations

This study has some limitations, including an analysis that was limited only to prescriptions and did not include socio-demographic analysis to compare drug incompatibilities among patient's categories. In addition, we only looked into chemical incompatibilities. More research is highly recommended to look into physical or physicochemical incompatibilities using either cross-sectional analysis or randomized clinical trials. Future research is also needed to gain a better understanding of IV chemical errors and their implications in clinical settings. It is also critical to develop novel research lab tests to detect physiochemical incompatibilities in untested combination therapies. Our study also suggested that similar research be conducted in multiple settings to improve the efficacy and safety of IV drug combinations. It is extremely crucial to raise awareness of compatibility issues among medical practitioners, have clinical pharmacists evaluate daily prescriptions, and provide accurate evidence and data that may help to reduce compatibility problems on the wards.

5. CONCLUSION

According to the study's findings, the majority of IV drug admixture was chemically incompatible, and the most commonly prescribed drugs in the study area were vitamin C, vitamin B complex, pantoprazole, and ceftriaxone respectively. The current study's intravenous combinations practices deviated significantly from the standards recommended, either by giving incompatible combinations or prescribing undocumented admixtures whose compatibility status is unknown. Future research is needed to gain a better understanding of the chemical incompatibilities between intravenous drugs.

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7. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

8. Ethical approval

All aspects and protocols of this study were reviewed and approved by faculty of pharmacy, Sana'a University and all targeted hospitals.

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10. Availability of Data

Data and materials are available upon request.

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