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Profile of Intravenous Admixture Drugs in Newborn Patients at Dr. Moewardi General Hospital Surakarta

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ABSTRACT

Intravenous admixtures are sterile solutions prepared by mixing one or more different drugs with a suitable solvent and given to patients via the intravenous route. One of the factors causing contamination of the intravenous preparation mixture is an error in the aseptic technique during the preparation phase. Errors in aseptic techniques can cause infection. Newborns (neonates) are children under the age of 28 days. During 28 days of birth, have the highest risk of dying. The rate of potential adverse drug events (ADE) is three times higher in children than adults and substantially higher in neonates receiving intensive care. Intravenous admixture therapy, often performed in general wards, is highly susceptible to bacterial contamination which can result from aseptic technique errors. Bacterial contamination in intravenous preparations can cause infection which can trigger septic shock to death. The purpose of this study was to evaluate the suitability of the mixing process and the process of administering intravenous admixture drugs to infant patients. This study was conducted on infant or neonatal patients who were hospitalized in general wards and special intensive wards for babies in hospitals. Dr. Moewardi Surakarta. The research took place from February to March 2020 and was carried out using a prospective observational method. The inclusion criteria for this study were patients receiving parenteral drug therapy with complete medical records. Analysis of drug miscibility/insolubility was carried out using Handbook an Injectable Drugs edition 17 as the main reference and ASHP Drug information handbook 2021 edition. The results of this study, the percentage of solubility of injectable drugs that dissolved was 44 times administration (36.7%). For the administration of insoluble drugs 3 times (2.5%) and 73 (60.8%) administrations there was no information regarding the solubility of the drugs given. The study concludes that although there is incompatibility potential information references, at the direct observation was no incompatibility found. The administration of the two potentially insoluble drugs was carried out with different syringe containers.

Keywords: Compatibility, incompatibility, intravenous drugs administration, newborn

Introduction

Intravenous drug administration is very prone to errors (Lyons et al., 2018). Errors in medication or medication errors are a common problem, especially in terms of prescribing and giving to patients. The average prevalence of medication errors occurs between 8-10% in developed countries. Meanwhile, the prevalence of medication errors in developing countries is 2.5-18.4% and the mortality rate has increased by 30%. This is due to poor health systems and infrastructure and limited human resource capabilities (Nguyen et al., 2015). The biggest error was in the drug administration process (23.5%). The results of a systematic review of 34 articles regarding errors in the preparation of parenteral drugs were labelling errors (0-99.0%) and inadequate aseptic technique (0-92.7%). At the stage of intravenous drug administration, there is an error of 60%. The error that often occurs in the administration process is incomplete labelling (60.1%) (Schnock et al., 2016).

Errors in the process of preparing intravenous mixtures can be caused by the large workload of nurses and fatigue at work which causes reduced concentration so that adherence to the application of aseptic technique procedures is low (Suvikas-Peltonen et al., 2017). At this time, there is still very little research related to intravenous mixture contamination conducted inwards and in pharmaceutical environments. The United States has implemented the mixing of intravenous preparations in the pharmaceutical environment which is carried out by pharmacists. This is in contrast to European countries which still carry out mixing in the wards and it is carried out by nurses. For this reason, training for nurses is needed regarding the mixing process and procedures for using safe intravenous administration equipment as well as education on the risks that can arise as a result of aseptic technique errors (Campino et al., 2017).

Newborns (neonates) are children under 28 days of age and have the highest risk of dying. Neonates are a very vulnerable population and have a high chance of experiencing the risk of unwanted side effects because the body's metabolic system is not yet perfect so therapy errors must be minimized so that adverse drug events (ADE) can be avoided. The level of potential ADE is three times higher in children than adults and substantially

higher in neonates in the NICU (Arumugam et al., 2016). In addition, neonates in the intensive care unit are affected by the availability of sufficient drugs. This can affect the quality and safety of the care of patients with very low birth weight babies (Ziesenitz et al., 2019).

Drug incompatibility is a physical reaction or an unexpected chemical reaction. This reaction occurs between two or more drugs when the mixing process is carried out in the same syringe, or vial or carried out with the same solution. This insolubility can occur between the drug and the diluent or between the drug and the drug and the packaging material with the drug. Chemical reactions are caused by molecular changes. These molecular changes are considered significant when more than 10% of one or more components are degraded. Reactions that occur physically cause changes such as changes in colour, preparation consistency, phase separation or emulsion rupture and gas production.

Potential complications due to the administration of insoluble drugs, precipitating drugs, and occlusions include central venous catheter (CVC) malfunction, decreased potential drug efficacy, embolism and local and even systemic inflammatory reactions. Information on clinical manifestations of drug precipitation or insolubility is still very limited. Other risks from handling improper catheter use besides occlusion are venous thrombosis, sepsis, chronic venous insufficiency, and pulmonary embolism (Maison et al., 2019). The importance of research related to the accuracy of dispensing and administering intravenous drugs due to the high prevalence of intravenous therapy used in hospitals for inpatients and related to the relationship between the accuracy of intravenous drug preparation and the incidence of mismatches in infants has not been widely carried out. The role of the pharmacist is expected to reduce the number of errors in the preparation of intravenous mixed preparations and increase the safety of treatment in infant patients. The research was conducted at the Dr. Moewardi General Hospital Surakarta. This study aimed to evaluate the suitability of the mixing process and the administration process and determine the factors that influence the inaccuracy of the mixing process and the process of administering intravenous admixture drugs to infant patients.

Method of Research

Type of research is observational. Data are presented as descriptive percentages with a cross-sectional design through prospective data tracing of patients treated in the neonatal HCU ward and NICU who received admixture intravenous preparations at the Dr. Moewardi General Hospital Surakarta. The assessment was carried out on the suitability of the preparation stage and the stage of administering intravenous admixture drugs to patients. The population in this study was taken from neonatal patients who received intravenous therapy at the Dr. Moewardi General Hospital Surakarta February-March 2020. Determination of the sample in this study used a proposive sampling technique, namely all patients who were treated in general and intensive care special wards for babies at the time of the study and met the study's inclusion criteria. The inclusion criteria in this study were (1) all infant or neonatal patients who were hospitalized in the general ward and special baby intensive ward at the Hospital. Dr. Moewardi Surakarta (2) patients received parenteral drug therapy (3) patients with complete medical records. While the exclusion criteria in this study were patients who died less than 12 hours after receiving injection drug therapy and patients who received vesicant or cytotoxic drugs.

Tools and Materials

The research instrument was used to collect patient data in the form of patient data collection sheets consisting of observation sheets, and complete patient medical records. The instruments used to analyze the data were the 2009 Guidelines for Mixing Injectable Drugs and Handling of Cytostatic Preparations of the Directorate General of Binfar and Medical Devices, Handbook An Injectable Drugs Edition 17 and ASHP Drug Information Handbook 2021 Edition.

The Course of The Research

The research was carried out in the preparatory stages, making research proposals, making permits and administering the administration at the Dr. Moewardi General Hospital Surakarta and in the implementation phase, researchers identified patients who fit the inclusion criteria and researchers made direct observations of the dispensing process (mixing) and the process of drug administration. The ethical clearance of this research was number 1.478/XII/HREC/2019 form Health Research Ethics Comitte Dr. Moewardi General Hospital.

Data Analysis

Analysis in this study will describe patient demographics, characteristics of the patient's main diagnosis, characteristics of injection drug use and the percentage of compatibility and incompatibility mixing frequency of non-cytotoxic injectable drugs.

Results and Discussion

This study was conducted in the inpatient high care unit (HCU) and neonatal intensive care unit (NICU) for neonatal (infant) patients at the Regional General Hospital. Dr. Moewardi Surakarta. The research took place from February to March 2020. The research was conducted in a prospective observational manner.

Table 1. Demographic characteristics of infant patients (Neonates) at Dr. Moewardi General Hospital Surakarta for the February-March 2020 period

Patient characteristics	Classification	Total	Percentage (%)
Gender	Men	9	30
	Female	21	70
Age (Kemenkes, 2016)	Neonatal perinatal (0-7 day)	18	60
	Advanced neonatal (8-28 day)	11	36,7
	Pasca neonatal (29 day-12 Month)	1	3,3
Length of stay	2-3 day	7	23,3
	4-7 day	14	46,7
	> 7 day	9	30
Ward	HCU Neonatus	15	50
	NICU	15	50

The number of patients observed in this study was 51 patients, but 30 patients met the inclusion criteria while 21 patients did not meet the inclusion criteria due to incomplete medical record data.

Demographic Description of Infant Patients (Neonates)

In this study, the results of data analysis on demographic characteristics were divided into gender, age, length of stay and treatment room which can be seen in table 1. Table 1 describes the demographic characteristics of 30 neonatal patients with 9 male patients (30%) and 21 female patients (70%). The percentage of female neonate patients is higher than the percentage of male infant patients. This sex percentage is different from the sex percentage in a study conducted in the neonatal intensive ward in an Ethiopian hospital, regarding hypothermia in neonates, there were 204 male neonates (57.3%) and 152 (42.7%) of neonatal patients are female (Demissie et al., 2018).

The age of neonatal patients in this study was divided into three groups. This age division is based on the standard neonatal age classification by the Ministry of Health of the Republic of Indonesia (2016), namely, the first group is early neonatal or perinatal aged zero to seven days. Patients who fall into this category are 18 people (60%). The second age category of neonatal patients was advanced neonatal with an age range of eight to twenty eight days, totalling 11 patients (36.7%). The last neonatal age category was post-neonatal with an age range of 29 days to 12 months in one patient (3.3%).

The length of the patient's hospitalization period in this study was divided into three ranges, namely for two to three days for seven patients (23.3%). The second period of hospitalization was four to seven days which was the period of hospitalization with the most patients, namely 14 patients (46.7%). The last hospitalization period had a range of more than seven days of treatment, with variations in hospitalizations for 8 days, 13 days, 14 days, 15 days, 16 days, 20 days, 29 days and 33 days with total patients treated spanning more than seven days was 9 patients. The length of care for neonatal patients will have an impact on the financial burden on parents or families. Parents' financial burden will be even heavier if their baby is treated for an increasingly long term. The costs that must be incurred are in addition to hospital treatment costs, the cost of purchasing medicines that run out and daily expenses such as transportation and food costs (Mengesha et al., 2022). In this study, the number of patients treated in the incentive ward and the general care ward for neonatal patients was the same. It is known based on data from Table 1, neonatal patients were treated in two different treatment rooms, namely the neonatal high care unit (HCU) for 15 patients (50%) and the Neonatal Intensive Care Unit (NICU) for 15 patients (50%).

Main Diagnostic Characteristics of Neonatal Patients

Table. 2 is a table that describes the characteristics of the disease of infant patients (neonates) based on the main diagnosis. The main diagnosis is a final diagnosis made by a doctor in the last episode of treatment which requires the patient to receive further treatment or examination. The definition of the main diagnosis is explained in the Regulation of the Minister of Health of the Republic of Indonesia Number 76 of 2016 which regulates the Guidelines for Indonesian Case Base Groups (INA-CBGs) in the Implementation of National Health Insurance.

The category of disease for the main diagnosis that mostly affects neonatal patients in this study is systemic infection with a percentage of 16.67%. The main diagnoses included in this category were neonatal infection and neonatal sepsis with a total of five cases. The main diagnosis with the next highest prevalence was neonatal sepsis with atresia ani in five cases (16.67%).

In other studies, neonates may experience rapid onset of sepsis and late onset of sepsis. A total of 123 (64.7%) neonates had early-onset sepsis and 67 (35.3%) had late-onset neonatal sepsis out of a total of 244 neonates. Another fact related to the incidence of sepsis in neonates was that as many as 22 neonates out of 244 samples (9%), their mothers had a history of urinary tract infections.

Table 2. Disease characteristics of infant patients (Neonates) based on main diagnoses at Dr. Moewardi General Hospital Surakarta period February-March 2020

Disease category	Main diagnosis	Total	Percentage (%)
Systemic infection	1. Infection neonatal 2. Neonatal sepsis	5	16.67
Systemic infection + congenital malformation of the Digestive system	Neonatal sepsis + atresia ani	5	16.67
respiratory system disease	Respiratory disorder moderate + congenital pneumonia	5	16.67
Systemic infection + respiratory system disease	1. Sepsis ec. candida parapsilosis + pneumonia 2. Neonatal sepsis with moderate respiratory distress ec. HMD grade II 3. Neonatal infection + mild respiratory distress	4	13.33
Gastrointestinal system disease	Necrotizing enterocolitis grade III	3	10
Systemic infection + other health problems in perinatal : jaundice neonatorum neonatal	Sepsis + hyperbilirubinemia	2	6.67
Electrolyte balance disorders	Electrolyte imbalance	1	3.33
Systemic infection + respiratory tract disease + other perinatal health problems: septic neonatal seizures	Sepsis + pneumonia + neonatal sepsis seizures ec. candiac parasilosis	1	3.33
Congenital malformation	Hydrocephalus	1	3.33
Health problems related to	LBW (low birth weight)	1	3.33
Other perinatal health problems: neonatal seizures + congenital malformations	Neonatal seizures	1	3.33
Respiratory system disease + congenital abnormalities of bones, joints and muscles	Bronchopneumonia + dysplasia suspected. streptopomonas candida	1	3.33

Meanwhile, of the 22 neonates whose mothers had a history of UTI, 14 of them (5.7%) had neonatal sepsis. Respiratory system disease was one of the most common categories in this study with a percentage of 16.67 or as many as 5 cases diagnosed with moderate respiratory distress with congenital pneumonia. In addition, there are cases of systemic infection accompanied by respiratory system disease. This condition was found in 4 cases (13.33%).

Characteristics of Injection Drug Use in Neonatal Patients

An overview of the class or class of drug therapy used in neonatal patients in this study can be seen in Table 3. The drug class with the highest prevalence used as electrolytes. The total use of electrolytes is 294 times or as much as 38%, followed by the use of glucose therapy classes. The third class of drug therapy that is frequently used is antibiotics. The use of the antibiotic therapy class in this study was 16.6%, followed by the use of the bronchodilator class of drugs as much as 9.1%. Percentage of use of antibiotic therapy class. high in third place 128 times (16,6%), is an illustration of the most common disease pattern suffered by patients, namely systemic infections.

The use of drugs with the highest prevalence in this study were calcium gluconate and potassium chloride with the frequency of each use being 144 times (18.6%). Both of these drugs are electrolytes. A study to monitor the effect of electrolyte use on reducing mortality and reducing hospital stays showed that potassium given at the beginning of the hospitalization period for newborns in intravenous fluids significantly reduced mortality and length of stay (Tasleem Bano et al. .al, 2022).

Characteristics of the number of injection drug use per day in neonatal patients in hospitals. Dr. Moewardi Surakarta can be seen in table 4. The table illustrates that the majority of injection drug use per day in one patient is more than 3 injection drugs.Injectable drugs given more than three drugs per day were 91 per cent or as many as 132 times. The administration of injection drugs per day with a range of one to three drugs per day is only given 13 times (9%)

Characteristics of Immiscibility and Miscibility of Drugs

Solubility characteristics of non-cytotoxic injectable drugs in neonates are presented in table 5. based on the type of solubility which was analyzed using the reference of Handbook on Injectable Drugs - ASHP 17th edition or published in 2013 and 2021 edition.

In this study, the percentage of solubility of the soluble injection drug was 44 times administration (36.7%). For the administration of insoluble drugs as many as three times (2,5%) and as many as 73 (60.8%) administrations, there was no information about the solubility of the drug given.

Table 3. Patterns of use of non-cytotoxic injection drug therapy groups in infant patients (neonates) at Dr. Moewardi General Hospital Surakarta for February-March 2020 period based on the 17th edition of the Injectable Drugs Guide

Group/Class Therapy	Frequency Therapy (N)	*Percentage (%)*
Electrolytes	294	38
Glucose	144	18,6
Antibiotics	128	16,6
Bronchodilators	70	9,1
Analgesic/antipyretic	55	7,1
Cardiovascular	34	4,4
Diuretics	13	1,7
Anti-fungal	11	1,4
Anti-epileptic	10	1,3
Hypotics/sedatives	7	0,9
Proton pump inhibitor (PPI)	5	0,6
Corticosteroids	1	0,1
Vitamins	1	0,1
Total	773	100

**N=overall frequency observed during the mixing process.*
***= one patient can get more than 1 time of intravenous drug administration*

Table 4. The number of injectable drug uses per day for infant (Neonate) patients at RSUD. Dr. Moewardi Surakarta period February-March 2020

Number of Medicines Per day (Item)	Total	Percentage (%)
1 - 3	13	9
> 3	132	91
Total	145	

Table 5. Overview of solubility of injectable drug administration for infants (neonates) based on ASHP 17th edition (Trissel, 2013) and solubility information according to ASHP Injectable Drug Information Ed. 2021 at RSUD. Dr. Moewardi Surakarta February-March 2020

Drug solubility	Total	Percentage (%)
Compatible (C)	44	36,7
Incompatible (I)	3	2,5
No information available (NI)	73	60,8
Total	120	

Table 6. Solubility patterns of non-cytotoxic injection drugs for infants (neonates) based on ASHP 17th edition (Trissel, 2013) and Solubility Information according to ASHP Injectable Drug Information Ed. 2021 at RSUD .Dr. Moewardi Surakarta Period February-March 2020

No.	Drug Name Given During Observation	Solubility Information Handbook On Injectable Drugs ed.17th (Trissel, 2013)	Solubility Information According to ASHP Injectable Drug Information Ed. 2021	Frequency of Giving	Percentage (%)
1	Aminophyline-Cepefime-Paracetamol	NI	NI	1	0,8
2	Ceftazidime	C	C	1	0,8
3	Furosemid-Dexamethason	C	C	1	0,8
4	Aminophyline-Fluconazole	C	C	2	1,7
5	Ampisilin	C	C	2	1,7
6	Cefepime	C	C	2	1,7
7	Paracetamole-Gentamicin-Phenytoin	NI	NI	2	1,7
8	Parcetamol	C	C	2	1,7
9	Aminophyline-Cepefime	I	I	3	2,5
10	Ampisilin Sulbactam-Phenytoin	NI	NI	3	2,5
11	Fluconazole-Paracetamol	NI	NI	3	2,5
12	Phenytoin-Paracetamol	NI	NI	3	2,5
13	Meropenem-Paracetamol-Metronidazole	NI	NI	4	3,3
14	Aminophyline-Paracetamol-Meropenem	NI	NI	6	5
15	Ceftazidime-Paracetamol	NI	NI	6	5
16	Furosemid	C	C	6	5
17	Meropenem-Amynophyline	C	C	6	5
18	Meropenem-Paracetamol	NI	NI	6	5

No.	Drug Name Given During Observation	Solubility Information Handbook On Injectable Drugs ed.17th (Trissel, 2013)	Solubility Information According to ASHP Injectable Drug Information Ed. 2021	Frequency of Giving	Percentage (%)
19	Gentamicin	C	C	7	5,8
20	Metronidazole-Paracetamol	NI	NI	7	5,8
21	Aminophyline	C	C	15	12,5
22	Aminophyline-Paracetamol	NI	NI	15	12,5
23	Aminophyline-Gentamicin	NI	NI	17	14,2
				120	**100**

Description: *Compatible (C), Incompatible (I), No information available (NI)*

Data regarding compatibility for most drugs used in are neonates are lacking. Therefore, special observations are needed in the selection of infusion lines for co-administered drugs. A more in-depth study of drug compatibility can be used to reduce the potential for unwanted events and toxicity and avoid occlusion of the infusion line in neonates who are in critical condition (Klikstad, et.al, 2010).

In this study, the drugs that had the highest prevalence and were administered at the same time were aminophylline and injection gentamicin. Information on potential incompatibility was not found between these two drugs in ASHP 2013 or AHSP 2021. Administration of aminophylline and gentamicin observed in the same observation period occurred 17 times or 14.2%. Information on potential incompatibility is found in the administration of aminophylline and cefepime as three times (2,5%), potential incompatibility of the administration of these two drugs can occur if these two drugs are mixed in the same syringe.

Conclusion

There is no difference in the results of the compatibility and in compatibility analysis based on the two references used (AHSP 2013 and AHSP 2021). According to the 2013 AHSP and AHSP 2021, the potential for drug mismatch between cefepime and aminophylline was observed three times (2.5%), but at the time of direct observation, the two drugs were compatible because the two drugs were prepared in different syringes.

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