

The relationship between polypharmacy and the incidence of drug interactions in pediatric inpatients at the regional general hospital (RSUD) Embung Fatimah Batam city

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ABSTRACT

Polypharmacy is one of the risk factors for potential drug interactions that can cause unwanted drug reactions and can also increase the risk to pediatric patients. This study aims to see if there is a relationship between polypharmacy and the incidence of drug interactions in pediatric inpatient prescriptions that will be carried out at Embung Fatimah Regional General Hospital, Batam City. This study uses a cross-sectional method, an observational research design conducted to determine the relationship between polypharmacy as the independent variable and the incidence of drug interactions as the dependent variable, with measurements taken at a single point in time. The target population to be studied is the total number of inpatient pediatric prescriptions at Embung Fatimah Hospital as many as 440 prescriptions. The sample used in this study was taken from the affordable population with inclusion and exclusion criteria. Polypharmacy prescriptions for pediatric inpatients at Embung Fatimah Regional General Hospital (RSUD) Batam City based on the results of research from a total of 168 prescriptions there were 123 (73.2%) polypharmacy prescriptions and 45 non-polypharmacy prescriptions. Drug interactions in pediatric inpatient prescriptions at the Regional General Hospital (RSUD) Embung Fatimah Batam City based on the results of the study from a total of 168 prescriptions there were 44 prescriptions experiencing drug interactions and 124 did not experience drug interactions. There is a significant relationship between polypharmacy and the incidence of drug interactions in pediatric inpatients at Embung Fatimah Regional General Hospital (RSUD) Batam City. The Chi-Square test resulted in a P-value ≤ 0.05 , indicating that the null hypothesis (H_0), which states that there is no relationship between polypharmacy and drug interactions, is rejected. Consequently, the alternative hypothesis (H_1), which states that polypharmacy is significantly associated with the incidence of drug interactions, is accepted.

Keywords: polypharmacy, drug interaction, pediatric, patients

ABSTRAK

Polifarmasi merupakan salah satu faktor risiko terjadinya potensi interaksi obat yang dapat menyebabkan reaksi obat yang tidak diinginkan dan juga dapat meningkatkan risiko terhadap pasien pediatrik. Penelitian ini bertujuan untuk melihat apakah ada hubungan antara polifarmasi dengan kejadian interaksi obat pada resep pasien rawat inap pediatrik yang akan dilakukan di Rumah Sakit Umum Daerah Embung Fatimah Kota Batam. Penelitian ini menggunakan metode cross-sectional, yaitu desain penelitian observasional yang dilakukan untuk menentukan hubungan antara polifarmasi sebagai variabel independen dan kejadian interaksi obat sebagai variabel dependen, dengan pengukuran dilakukan pada satu titik waktu. Populasi target yang akan diteliti adalah jumlah seluruh resep pediatrik rawat inap yang ada di RSUD Embung Fatimah sebanyak 440 resep. Sampel yang digunakan dalam penelitian ini diambil dari populasi terjangkau dengan kriteria inklusi dan eksklusi. Resep polifarmasi pasien rawat inap pediatrik di Rumah Sakit Umum Daerah (RSUD) Embung Fatimah Kota Batam berdasarkan hasil penelitian dari total 168 resep terdapat 123 (73,2%) resep polifarmasi dan 45 resep tidak polifarmasi. Interaksi obat pada resep pasien rawat inap pediatrik di Rumah Sakit Umum Daerah (RSUD) Embung Fatimah Kota Batam berdasarkan hasil penelitian dari total 168 resep terdapat 44 resep mengalami interaksi obat dan 124 tidak mengalami interaksi obat. Terdapat hubungan yang signifikan antara polifarmasi dan kejadian interaksi obat pada pasien anak rawat inap di RSUD Embung Fatimah Kota Batam. Uji Chi-Square menghasilkan nilai $P \leq 0,05$, yang menunjukkan bahwa hipotesis nol (H_0), yang menyatakan bahwa tidak ada hubungan antara polifarmasi dan interaksi obat, ditolak. Dengan demikian, hipotesis alternatif (H_1), yang menyatakan bahwa polifarmasi berhubungan secara signifikan dengan kejadian interaksi obat, diterima.

Kata Kunci: Polifarmasi, Interaksi, Pediatrik, Rumah Sakit, Embung Fatimah

1. INTRODUCTION

Clinical pharmacy is the responsibility of a pharmaceutical worker or pharmacist in identifying potential and solving drug-related problems aimed at improving the quality of life of patients, avoiding drug-related problems and solving drug-related problems. *Drug-related problems (DRPs)* can be defined as a condition related to drug therapy that actually or potentially interferes with desired clinical outcomes. These drug-related problems (*DRPs*) usually occur in hospitalized patients, which can lead to an increase in hospital stays. According to [1] based on the *American Society of Hospital Pharmacist (ASHP)* *DRPs* are classified based on several types, namely: untreated indications, inappropriate drug selection, subtherapeutic doses, failure to receive drugs, overdose, drug side effects, drug interactions and use of drugs without indications. Drug-related problems also occur at the Embung Fatimah Regional General Hospital (RSUD). Based on the prescription data for inpatient pediatric patients available in the medical records of the Embung Fatimah Regional General Hospital (RSUD) from January to December 2022, there were 526 polypharmacy prescriptions.

Several studies in Indonesia on drug-related problems in pediatric patients have reported the percentage of different *DRP* categories. A study conducted by [2], which showed the number of drug *related problems* with a percentage of drug interactions as much as 58.3%, less drug dosage as much as 30%, more drug dosage as much as 10% and drugs without indications 0%. Whereas in a study conducted by [3], the results were obtained with a percentage of drug interaction events as much as 56.40%, too small doses as much as 24.42%, non-compliance as much as 9.88%, inappropriate drugs as much as 7.56% and ADR as much as 1.74%. Based on these 2 studies, it is known that *drug* interaction is a category of *drug related problems* with the highest percentage among several other categories. Drug interaction itself is a state of change in the effect of a drug due to the presence of other drugs, food, drinks, herbs, or chemicals in the environment [4]. Drug interactions are also considered clinically important if they result in increased toxicity or reduced effectiveness of the interacting drug, especially when it comes to drugs with a narrow therapeutic index[5].

Some factors that can lead to drug interactions include intentional misuse or lack of knowledge about the active ingredients contained in drugs [6]. Another important factor that can also cause drug interactions is polypharmacy[7]. Polypharmacy is the use of more drugs than medically necessary and can increase the risk of drug interactions. Some types of polypharmacy are duplication, *opposition*, and *alteration* Polypharmacy itself is one of the world's health problems. The impacts that can be caused by polypharmacy include increased health costs, drug side effects, non-compliance and others. In a population-based study, it was found that patients who used more than 5 drugs increased the risk of experiencing side effects by 88%, compared to patients who used fewer drugs [8].

Polypharmacy is not the same as inappropriate prescribing, but the two are interconnected. Therefore, a validated process is needed to see whether the prescription is appropriate or not. On the study of potential drug interactions in polypharmacy prescriptions in two Bandung City pharmacies out of 1218 prescription

sheets, 896 sheets were included in the inclusion criteria with 569 prescription sheets (63.50%) experiencing potential 5-drug interactions. Based on severity, the majority of interactions were moderate (85.60%), minor interactions (9.28%), and major interactions (5.12%). Meanwhile, based on the mechanism, the majority of drug interactions were pharmacodynamic interactions (90.34%), and pharmacokinetic interactions (9.66%).

Judging from the number of potential drug interactions, it is best to avoid polypharmacy prescribing and handling potential drug interactions that can occur. One of the treatments that can be done is by conducting a drug review. Drug review can be carried out by doctors and clinical pharmacist. Drug review aims to improve therapeutic *outcomes* and minimize the risk of side effects due to drugs, which aims to improve patient safety so that the *patient's quality of life* is more secure. Based on data from General Hospital (RSUD) Embung Fatimah Batam City in 2022 is 1,266 patients with an age range of 0-18 years. Meanwhile, the total number of polypharmacy prescriptions for pediatric inpatients in 2022 at the RSUD was 526 polypharmacy prescriptions. Based on this background, the author is interested in further research on the identification of potential drug interactions in polypharmacy prescriptions for pediatric inpatients at Embung Fatimah Regional General Hospital (RSUD) Batam City.

2. MATERIALS AND METHODS

This study employs an analytic approach using a cross-sectional design, an observational research design conducted to determine the relationship between polypharmacy as the independent variable and the incidence of drug interactions as the dependent variable, where measurements are taken at one time (simultaneously). The population in this study consisted of 440 inpatient pediatric prescriptions at Embung Fatimah Hospital, selected using purposive sampling. The inclusion criteria were prescriptions for pediatric patients from inpatient polyclinics between June and August 2023, prescriptions from general services and BPJS (where prescriptions containing two or more of the same drug were counted as a single medication), and prescriptions containing TB antibiotics (Rifampicin, Isoniazid, Pyrazinamide). Exclusion criteria included prescriptions containing topical drugs such as creams, ointments, gels, eye drops, ear drops, and nose drops, as well as prescriptions from the emergency department, haemodialysis installation, and medical rehabilitation.

The required sample size was determined using the cross-sectional formula with a margin of error (d) of 0.05, resulting in a total of 168 samples. The prescriptions were then reviewed using a clinical aspects worksheet to assess drug interactions in pediatric inpatients, utilizing the Medscape application and Stockley's Drug Interactions, Ninth Edition as references. The potential drug-drug interactions (DDIs) were calculated using the formula: $\% \text{ DDI} = (\text{Number of prescriptions with potential DDI} / \text{Total number of prescriptions}) \times 100\%$, where in this study, 44 out of 168 prescriptions were identified as having potential DDIs, resulting in a percentage of 26.2%. The relationship between polypharmacy and the incidence of drug interactions was further analyzed using the chi-square test in SPSS software to determine statistical significance.

3. RESULTS AND DISCUSSION

In the incidence of drug interactions in polypharmacy prescriptions for pediatric patients at Embung Fatimah Hospital, Batam City, the highest percentage of gender was found to be men (54.2%) while women was 45.8%. The results of this study are in line with research conducted by Wahyuni, et al [10], which shows that the prevalence of male patients is more than women because boys often do activities outside the home which allows boys to tend to be at greater risk of exposure to bacteria and infectious diseases compared to girls. The prescriptions studied totaled 168 prescriptions, with 156 prescriptions covered by health insurance and 12 being independent or general. The results showed that 123 prescriptions (73.2%) were classified as polypharmacy, while 45 prescriptions (26.8%) were non-polypharmacy. These findings align with research [1], which reported that 327 out of 400 patients (81.75%) received polypharmacy prescriptions, while the remaining 73 patients (18.25%) received non-polypharmacy prescriptions. The similarity in percentage distribution reinforces the reliability of our findings and highlights the persistent issue of polypharmacy in prescription patterns. The data were analyzed using descriptive analysis with SPSS software to determine the frequency and distribution of polypharmacy. Additionally, a chi-square test was performed using SPSS to assess the relationship between polypharmacy and the occurrence of drug interactions, these results can be seen in table 1.

Table 1. Characteristics of Polypharmacy and Drug Interaction Relationships in Pediatric Inpatients

Prescriptions	Frequency (n)	Percentage (%)
Gender		
Male	91	54,2
Female	77	45,8
Health insurance		
Other Assurance	12	7,1
BPJS	156	92,9
Polypharmacy	123	73,2
No-Polypharmacy	45	26,8
Drug Interactions	44	26,2
No Drug Interactions	124	73,8

Polypharmacy is the concurrent use of five or more drugs by a patient. While the use of 0-4 drugs is also called non-polypharmacy, concurrent use of 5-9 drugs is called polypharmacy, and the use of 10 or more is called excessive polypharmacy. However, topical medicines, herbs, vitamins, and minerals are not included in polypharmacy [11]. Polypharmacy is increasingly recognized as a common concern in pediatric patients with both potential benefits such as control of complex or multiple disease states and harms such as adverse drug effects, drug interactions, hospitalization, poor drug adherence, mortality, medical care burden and high healthcare costs. Despite the increasing use of polypharmacy in pediatrics, there is no uniform definition of polypharmacy in pediatric patients. Factors such as number and

duration of drugs, drug concordance, medical condition, and clinical setting are usually considered [12].

Based on table 1, it was found that drug interactions that occurred in pediatric inpatients at Embung Fatimah Hospital Batam City, as many as 44 out of a total of 168 prescriptions with a percentage (26.2%) prescriptions occurred interactions and 124 out of a total of 168 prescriptions with a percentage (73.8%) prescriptions that did not experience drug interactions. Based on these data, it can be calculated that the potential DDI's that occur is 26.2%. This result is slightly higher than the results of research conducted by Sulfiani Saula, 2019 which amounted to 20.10% [13], but still better when compared to research conducted by Rahayu, 2019 which reached 49.44% [14].

Table. 2 Frequency Distribution of Drug Interactions that most often appear in Pediatric Inpatients at Embung Fatimah Regional General Hospital, Batam City

No	Drugs Interactions	Number	Type of Interaction	Potential Effect
1.	Rifampicin - Isoniazid	18	Pharmacokinetics	Rifampicin increases isoniazid toxicity
2.	Rifampicin - Pyrazinamide	17	Pharmacokinetics	Both increase the toxicity of the other
3.	Isoniazid - Paracetamol	10	Pharmacokinetics	Concomitant use may result in increased risk of hepatotoxicity
4.	Isoniazid - Pyrazinamide	9	Pharmacodynamics	Both increase the toxicity of the other
5.	Captopril - Furosemide	4	Pharmacokinetics	Concomitant use may pose a risk of acute hypotension and renal insufficiency
6.	Paracetamol - phenytoin	3	Pharmacokinetics	Concomitant use may result in decreased effectiveness of paracetamol and increased risk of hepatotoxicity
7.	Valproate Acid- Phenytoin	3	Pharmacokinetics	Concomitant use may result in altered valproate acid levels or altered phenytoin levels
8.	Rifampicin - Paracetamol	2	Pharmacokinetics	Rifampicin decreases paracetamol levels by increasing metabolism leading to hepatotoxicity
9.	Furosemide - digoxin	2	Pharmacokinetics	Concomitant use may result in increased risk of digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
10.	Furosemide - Gentamicin	2	Pharmacokinetics	Concomitant use may result in increased plasma and tissue concentrations of gentamicin and additive ototoxicity or nefrototoxicity

Based on Table 2, the most frequent drug interaction in pediatric inpatients at Embung Fatimah Hospital, Batam City, was between rifampicin and isoniazid, with a total of 18 major interactions. When given simultaneously, this combination can increase hepatotoxicity, requiring close monitoring. A study involving 102 patients reported that 31% experienced liver damage due to this interaction. Rifampicin is a strong enzyme inducer, which accelerates the metabolism of isoniazid and increases its toxic metabolites, thereby heightening the risk of hepatotoxicity. Similarly, rifampicin

and pyrazinamide also pose a high risk of liver toxicity. Liver function tests should be routinely conducted in patients receiving these combinations, especially those with pre-existing liver conditions [5,15,16].

Other significant interactions were observed, including isoniazid with paracetamol, which enhances enzyme activity, leading to toxic paracetamol metabolites and an increased risk of liver damage. Patients on isoniazid therapy should avoid paracetamol or use alternative analgesics. If co-administration is necessary, liver function should be closely monitored [5]. The interaction between furosemide and captopril, although generally safe, may cause "first-dose hypotension," leading to dizziness or fainting. Additionally, furosemide can cause hypokalemia, which may be exacerbated when combined with captopril. In contrast, the combination of digoxin and furosemide can increase potassium and magnesium excretion, heightening the risk of digoxin toxicity. This side effect can be mitigated by administering potassium and magnesium supplements or using potassium-sparing diuretics [5].

Other notable interactions include paracetamol with phenytoin, which can alter paracetamol metabolism and cause severe liver toxicity. Similarly, valproic acid and phenytoin may interfere with each other's plasma levels, requiring careful dose adjustments. Rifampicin, as a CYP3A4 inducer, slightly reduces the therapeutic effect of paracetamol, though this interaction is classified as minor. However, liver function monitoring is still advised, particularly in patients with impaired liver function [Medscape]. Lastly, the combination of furosemide and gentamicin should be avoided due to the risk of additive nephrotoxicity and ototoxicity, except in life-threatening cases [17].

The relationship between polypharmacy and drug interactions

The statistical test results based on table 4.6 show that out of a total of 123 polypharmacy prescriptions, 39 of them experienced drug interactions and 84 other polypharmacy prescriptions did not experience drug interactions. While from a total of 45 prescriptions that were not polypharmacy, 5 of them experienced drug interactions and the other 40 did not experience drug interactions. statistical test results are depicted in table 3.

Table 3 Relationship between Polypharmacy and Drug Interactions in Pediatric Inpatients at Embung Fatimah Regional General Hospital, Batam City

Resep	Interaction Event				Total		P value	PR
	Interactions		No Interactions		N	%		
	N	%	N	%				
Polpharmacy	39	31,7	84	68,3	123	100	0,007	2,85
Non-Polypharmacy	5	11,1	40	88,9	45	100		

Based on these results, that most of the prescriptions for pediatric inpatients at Embung Fatimah Regional General Hospital (RSUD) Batam City are polypharmacy prescriptions with no drug interactions as many as 84 prescriptions (68.3%).The results of calculations using the *Chi-square test* showed a significant relationship between

Polypharmacy Prescriptions and Drug Interaction Events with a *P-value* of 0.007 where (*P-value* ≤ 0.05) so that it was rejected and accepted So it can be concluded that there is a significant relationship between Polypharmacy and Drug Interaction Events in Pediatric Inpatients at the Regional General Hospital (RSUD) Embung Fatimah Batam City. The results of the calculation of *Risk Estimate* in the *Chi-square test* obtained the result of PR 2.85. Based on this result, it can be interpreted that there will be a risk of drug interactions as much as 2.85 times if polypharmacy is found in pediatric inpatients at the Regional General Hospital (RSUD) Embung Fatimah Batam City.

4. CONCLUSION

Based on the research findings at Embung Fatimah Regional General Hospital (RSUD) Batam City, out of a total of 168 pediatric inpatient prescriptions, 123 (73.2%) were categorized as polypharmacy prescriptions, while the remaining 45 were non-polypharmacy prescriptions. Drug interactions in pediatric inpatient prescriptions at Embung Fatimah Regional General Hospital (RSUD) Batam City based on the results of the study from a total of 168 prescriptions there were 44 prescriptions experiencing drug interactions and 124 did not experience drug interactions. There is a significant relationship between polypharmacy and the incidence of drug interactions in pediatric inpatients at Embung Fatimah Regional General Hospital (RSUD) Batam City, with the *Chi-Square test* obtained value (*P-value* ≤ 0.05).

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