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Research Article

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Prevalence of Potential Drug-Drug Interactions in Neonatal Intensive Care Unit of a Tertiary Care Hospital: A Prospective Observational Study

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Abstract: Hospitalized neonates in neonatal intensive care unit (NICU) are usually exposed to great number of drugs and they are susceptible to adverse outcomes due to their immature functioning organs and reasons like inappropriate dosing or choice of medicines. We aimed to assess the prevalence and characteristics of potential drug- drug interactions (pDDIs) in the NICU. In this prospective observational study, case sheets of neonates who were in the NICU for more than 24 hours and were administered with at least two drugs were analysed for pDDIs by using Lexicomp database. All pDDIs were classified according to their severity, reliability, risk level and their underlying mechanisms. Potential predictors and potential outcomes of pDDIs were also evaluated. We found that 66.2% of neonates were exposed to at least one pDDI. Total of 902 pDDIs comprising of 70 distinct pDDIs were identified of which 88% were moderate in severity. 11.8% and 0.2% of them were major and minor respectively. Most of pDDIs belonged to category C (61.4%) and category D (30%) of risk level. Majority of interactions had pharmacodynamic mechanism (65.7%) and fair scientific evidences (68.6%). The most common potential adverse drug events included increased sympathomimetic effects, nephrotoxicity and alteration of serum concentration of drugs. Systemic anti-infective were involved in majority of interactions. pDDIs were more prevalent in neonates with gestational age of <32 weeks, ≥11 days of hospital stay and those who received ≥11 concomitant drugs. Identification of pDDIs and monitoring the neonates for potential adverse outcomes is mandatory especially in high risk conditions to avoid or minimize the actual harm.

Keywords: Potential drug-drug interaction, neonate, anti-infective, adverse outcomes, NICU

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1. INTRODUCTION

A drug-drug interaction (DDI) is defined as the modification of the effects of one drug (the object drug) by the prior or concomitant administration of another drug (the precipitant drug).[1] DDIs are one of the causes of adverse drug reactions (ADRs) and adverse drug events (ADEs) following multiple drug therapies.[2,3] Neonates hospitalised in neonatal intensive care unit (NICU) have multiple complications and/or are premature babies. Therefore they are exposed to more number of drugs and consequences of DDIs may be more serious in NICU patients.[4] DDIs which are identified theoretically (not actually occurred) and there are possibilities of altering effect of any concomitant administered drugs are termed as potential drug-drug interactions (pDDIs).[5,6]However, identification and early reporting of them and close monitoring of neonates exposed to such interactions is crucial to prevent subsequent ADRs, ADEs, increase in length of hospital stay and medication costs.[7,8] Hospitalised neonates are more susceptible to DDIs than adults and their subsequent adverse outcomes including ADRs, toxicity, therapeutic failure, etc.[9] This can be explained by immature functioning organs leading to different pharmacokinetic (absorption, distribution, metabolism and excretion) response to a drug. Off-label use of drugs in neonates and extrapolation of adult data on selection of doses of drugs for paediatrics are other factors exposing them to more adverse events following DDIs.[10-13] Majority of pDDIs are preventable and critical evaluation of medication charts to identify drug interactions in NICU and giving awareness to clinicians is necessary to improve effective and rational use of drugs and ensure patient safety. Unfortunately, among the studies that assessed pDDIs in intensive care units, there are very limited studies conducted in this field among hospitalised neonates in NICU which is highly significant, since they are vulnerable population with their special physiological condition. Therefore, this study was conducted to determine the prevalence of pDDIs in NICU to give awareness to clinicians about importance of pDDIs in critically ill neonates.

2. METHODS

This was a prospective study conducted in the NICU of a tertiary care teaching hospital in Bangalore for duration of 2 years from July 2017 to July 2019 after obtaining approval from Institutional Human Ethics Committee (dated 09/12/2016 with reference number of VIPS/IEC/2016-14). The informed consent was obtained from parents/ guardians of the study subjects. All neonates (both preterm and term) from the NICU and also all neonates who were not in-born but who had been referred from outside to NICU at the study hospital were included in this study. Neonates whose parents/ guardians refused or were unable to give valid consent and those cases with mortality within 24 hours of birth were excluded. All data including demographic details (gestational age, birth weight, gender, date of birth, postnatal age), admission and discharge dates, clinical indication, information about prescribed medicines in the NICU including indication, dose, frequency and route of administration and dosage form were collected from medical records of neonates and entered in the designed data collection form. Clinical progress of the neonates was documented until discharge from the hospital. All medication charts having at least two drugs were evaluated for potential pDDIs were classified on the basis of severity level (minor, moderate and major) and risk level (A: No known interaction B: No action needed C: Monitor therapy D: Consider therapy modification X: Avoid combination). Each of specified risk levels show the level of urgency in responding to interactions. Reliability rating (excellent, good, fair, and poor) also was assigned to each identified pDDI as per Lexicomp reliability rating classification to show level of evidence of each identified pDDI. Underlying mechanism (pharmacokinetic/pharmacodynamic) of pDDIs was assessed based on the available information in Lexicomp database. Neonatal diagnoses were classified according to ICD-10 (International statistical classification of diseases and related health problems 10th revision, 2016). All administered drugs were classified according to WHO Anatomical Therapeutic and Chemical (ATC) classification system.

3. STATISTICAL ANALYSIS

Analysis was done using the Statistical Package for Social Science (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). The collected data was analysed using descriptive statistics and results have been presented in terms of number, percentage and in terms of mean ± standard deviation. Chi-square test was used and level of significance was set as 0.05.

4. RESULTS

There were a total of 669 neonates admitted to NICU during study period of 2 years. Of these 669 neonates, 42 were excluded because they had received only phototherapy. Another 10 cases that were administered with only one drug were also excluded. Higher prevalence of male (58.5%) was observed compared to female neonates (41.5%). The demographic characteristics of 617 neonates who met the inclusion criteria and distribution of pDDIs among them are shown in the table No.1. We found higher exposure to at least one pDDI among male neonates (246, 68.1%) than female neonates (163, 63.6%). However, it was not statistically significant (P=0.247). According to gestational age, exposure to at least one pDDI was more among very preterm (41, 100%) and extremely preterm (5, 100%) compared to other groups and it was shown to be statistically significant ($p < 0.001$). The average length of hospital stay was 7.71 ± 6.42 (SD) days and the mean birth weight was 2.48 ± 0.68 (SD) Kg. The most frequent diagnoses were bacterial sepsis, respiratory distress, congenital malformation of circulatory system and slow fetal growth. The total number of prescribed drugs was 4640 and 76 different drugs were given. The average number of drugs per encounter was found to be 7.52. The most frequently prescribed classes of drugs as per ATC classification were systemic anti- infectives (class J), blood and blood forming organs class (class B) and alimentary tract and metabolism class (class A). Total of 902 pDDIs comprising of 70 distinct pDDIs were identified. Of these 902 pDDIs, 793 (88%) were moderate, followed by 107 (11.8%) major and 2 (0.2%) minor in severity. All these interactions were supported by excellent (4.3%), good (22.8%), fair (68.6%) and poor (4.3%) scientific evidence. With respect to risk level, most of pDDIs belonged to category C (43, 61.4%) followed by category D (21, 30%), category B (5, 7.1%) and category X (1, 1.4%). Detailed description of prevalence of pDDIs of different severity among neonates is given in Table No.2. It was found that most commonly observed major and moderate pDDIs

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resulted in 6.2% and 73.1% of all pDDIs respectively. Details of which are given in table No. 3. Some of potential ADEs of all identified interactions included nephrotoxicity, ototoxicity, alteration of serum concentration of drug, decrease in therapeutic effectiveness of drug, increased sympathomimetic effects, increased neuromuscular blocking effect, hyperkalemia, QTc interval prolongation, phenobarbital toxicity, etc.

Table 1. Characteristics of neonates and distribution of pDDIs

Characteristics	No. of patients (n)		Total (%)	X^2	P value
	With pDDI	without pDDI			
Gestational age					
Term (≥ 37 weeks)	192	154	346 (56.1)	50.940	<0.001 (significant)
Moderate to late preterm (32 to < 37 weeks)	171	54	225 (36.5)		
Very preterm (28 to < 32 weeks)	41	0	41 (6.6)		
Extremely preterm (< 28 weeks)	5	0	5 (0.8)		
Gender					
Male	246	115	361 (58.5)	1.341	0.247 (not significant)
Female	163	93	256 (41.5)		

Level of significance was set as 0.05.

Table 2. Prevalence of pDDI among neonates in NICU

Characteristics	No. of patients exposed to pDDI (n) (%)	Prevalence of pDDI (n) Major	Moderate	Minor	Total of pDDI (n)
Gestational age					
Term (≥ 37 weeks)	192 (55.5)	34	302	0	336
Moderate to late preterm (32 to < 37 weeks)	171 (76%)	29	308	1	338
Very preterm (28 to < 32 weeks)	41 (100)	35	147	1	183
Extremely preterm (< 28 weeks)	5 (100)	9	36	0	45
Total	409 (66.2)	107	793	2	902
Gender					
Male	246 (60.1)	72	483	1	556
Female	163 (39.9)	35	310	1	346
Total	409 (66.2)	107	793	2	902
Hospital stay (days)					
1-5	133 (43)	3	164	0	167
6-10	131 (82.9)	16	210	1	227
11-15	70 (94.5)	24	185	0	209
16-20	46 (100)	25	82	1	108
21-25	10 (100)	14	52	0	66
26-30	9 (100)	12	56	0	68
≥31	11 (91.6)	13	44	0	57
Total	409 (66.2)	107	793	2	902
Number of concomitant drugs					
2-5	117 (39.2)	2	136	0	138
6-10	173 (86.5)	6	253	1	260
11-15	66 (100)	19	148	0	167
16-20	32 (100)	27	120	0	147
≥21	21 (100)	53	136	1	190
Total	409 (66.2)	107	793	2	902

Table 3. Prevalence of most common identified pDDI

Drug- Drug combination	Potential ADE	Reliability	Risk level	Number of patients exposed	Exposure %
Major					
Linezolid + caffeine	Increase in hypertensive effect	Fair	D	19	2.1
Linezolid + adrenaline	Increase in hypertensive effect	Fair	D	11	1.21
Calcium gluconate (intravenous) + ceftriaxone	Formation of insoluble precipitate (contraindicated in neonates)	Fair	D	10	1.1
Amphotericin B + colistin	Increase in nephrotoxicity	Fair	D	6	0.66
Vancomycin + colistin	Increase in nephrotoxicity	Fair	D	6	0.66
Linezolid + salbutamol	Increase in hypertensive effect	Fair	D	4	0.44
Moderate					
Amikacin + piperacillin and tazobactam	Decrease in serum concentration of amikacin	Excellent	D	254	28.15
Amikacin + magnesium chloride (present in multiple electrolytes and dextrose intravenous fluid)	Increase in neuro-muscular blocking effect of amikacin	Poor	C	187	20.73
Gentamicin + piperacillin and tazobactam	Decrease in serum concentration of gentamicin	Excellent	D	95	10.53
Heparin + potassium chloride (present in multiple electrolytes and dextrose intravenous fluid)	Increase in hyperkalemic effect of potassium salts	Fair	C	52	5.76
Adrenaline + caffeine	Increase in adverse/ toxic effect of sympathomimetics	Fair	C	29	3.21
Adrenaline + dopamine	Increase in adverse/ toxic effect of sympathomimetics	Fair	C	16	1.77
Phenobarbitone + fosphenytoin	Increase in CNS depression of phenobarbitone	Fair	C	7	0.77
Dopamine + caffeine	Increase in adverse/ toxic effect of sympathomimetics	Fair	C	7	0.77
Domperidone + fluconazole	Increase in QTc prolonging effect	Fair	X	7	0.77
Amikacin + furosemide	Increase in adverse/ toxic (specifically ototoxicity, nephrotoxicity) of amikacin	Fair	C	6	0.66

C: Monitor therapy D: Consider therapy modification X: Avoid combination

5. DISCUSSION

To the best of our knowledge, studies reporting pDDI in neonates are very rare and this study was proposed to evaluate the prevalence and nature of pDDIs in NICU. So, we could compare our results to few similar studies conducted in infant and children population and not specifically in neonates. Overall, 66.2% of neonates were exposed to at least one pDDI which was much higher than the findings of another study conducted among pediatric population of all age groups in Czech Republic.[14]Some of the reasons of this variation could be the differences in study population and pattern of drug utilization. As our study population was limited to neonates and most of admitted neonates were preterm with critical conditions in NICU, they were exposed to multiple therapeutic regimens to survive which is a known risk factor for greater pDDI exposure. However, our estimation was similar to the findings of study of Rao C et al conducted in paediatric intensive care unit (PICU) in India.[15] We compared the prevalence of pDDIs with respect to gestational age, length of hospital stay and number of concomitant drugs. There was an inverse relationship between gestational age and exposure to pDDIs. Extremely preterm and very preterm neonates having different comorbidities received greater number of drugs for more number of days compared to term babies which can be considered as a risk factor for higher frequency of pDDIs among preterm babies. Rao et al, reported similar relationship between age and number of pDDIs whereas it was in contrast to other studies conducted in PICU and paediatric wards in which they reported increased likelihood of pDDIs with increase in age.[14-17] Our findings showed that pDDIs was more prevalent among neonates who had ≥ 11 days of hospital stay. Similarly, other studies conducted in the United States found higher likelihood of pDDI exposure among patients who had longer length of hospital stay.[17,18] With respect to number of drugs, all patients who received ≥ 11 drugs and 86.5% of neonates received 6-10 drugs concurrently were exposed to pDDIs. This comparison shows a direct relationship between number of prescribed drugs and pDDIs exposure. Similar findings were reported by other studies in India and Pakistan where increase in polypharmacy was associated with higher prevalence of pDDIs.[15,16] As it is mentioned earlier, of all identified pDDIs, most interactions were moderate in severity followed by major and minor. Similar consequence of severity of pDDIs was reported by Ismail M et al.[16] Though major pDDIs were less common in our study, giving awareness to clinicians about their serious risks was our main priority to avoid harmful outcomes among neonates.

Interaction of intravenous calcium gluconate and intravenous ceftriaxone injection was one of the major pDDIs (contraindicated in neonates) that was reported to clinicians. This interaction can lead to death due to formation of insoluble precipitation in kidney and lung. Though clinicians could not change the therapy, they agreed for sequential administration of two drugs and flushing the infusion line with compatible fluid between two administrations to avoid the risk. We found only 2 minor pDDIs of category B that they did not require clinician's attention and they were of academic concern. According to the drugs prescribed, we found that systemic anti-infectives (amikacin, gentamicin, piperacillin and tazobactam, linezolid, ceftriaxone, fluconazole, amphotericin B, colistin) followed by respiratory system class of drugs (caffeine, adrenaline, salbutamol) and cardiovascular system class of drugs (dopamine, furosemide) were the most frequently interacting drugs. Majority of the above drugs are important in the management of the clinical status of the neonates. Similar observations were reported by other studies where antihypertensives, antimicrobials and drugs of respiratory system were frequently involved in pDDIs.[15,19] However, in study of Langerva P et al, antiepileptics and immunosuppressant were most frequently drugs involved in pDDIs.[14] In the present study, of all systemic anti-infectives, linezolid and aminoglycosides were involved in various types of commonly identified pDDIs. The most common interaction of linezolid was with sympathomimetics with potential for increase in hypertensive effect. We found that interactions of aminoglycosides together or with other anti-infectives (including colistin) or with furosemide with potential for enhanced nephrotoxicity were commonly identified interactions. The most frequently identified pDDIs of aminoglycosides was with piperacillin and tazobactam (excellent level of evidence) in which the potential ADE (decreased serum concentration of aminoglycoside) could be preventable by avoiding administration of both drugs through the same intravenous line. Same was reported to clinicians. In other studies, benzodiazepine (midazolam) was one of the drugs involved in most of pDDIs in PICU[15,18];whereas in our study midazolam was implicated in small fraction of pDDIs (0.5%). Generally, midazolam was not the widely used drug to induce sedation in our study population in NICU due to its known adverse outcomes among neonates. Therefore, underlying medical conditions and patient population could be the probable reasons for these variations among different studies. Our findings showed that prevalence of pDDIs was higher in neonates diagnosed with bacterial sepsis of newborn, respiratory distress of newborn and congenital malformation of the circulatory system. However, Langerva P et al found that patients diagnosed with epilepsy, lymphoid leukemia and arthritis were at greater risk of pDDIs.[14] In regard to assessment of underlying mechanism associated with pDDIs, the majority of interactions were pharmacodynamic (65.7%) and 31.4% of were pharmacokinetic drug interactions. 2.9% of pDDIs were of both pharmacokinetic and pharmacodynamic interactions. Similar findings were reported by other studies with most interactions based on pharmacodynamic mechanism.[15,19] This study revealed the prevalence of pDDIs in NICU and highlighted the most frequently identified drug interactions with their level of risks and severity. As studies of drug interaction in neonates are very rare, findings of our study can improve clinical outcomes in neonates by giving awareness to clinicians and encouraging them to monitor drug interactions and their potential outcomes closely. The limitation of our study was the difficulty to confirm clinically occurred ADEs, as our study population were neonates most being critically ill and with immature functioning organs. This matter made the assessment of actual occurrence of such potential adverse events challenging.

6. CONCLUSION

Occurrence of pDDIs is common in NICU, as the preterm and critically ill term neonates are exposed to high number of drugs during their hospitalisation period. Age, number of drugs and length of hospital stay were factors linked with higher prevalence of pDDIs. Patients with these predictors may require more attention and daily monitoring in order to avoid adverse outcomes. Identification of pDDIs and reporting the high-risk drug interactions to clinicians, proper use of drug combinations and close monitoring of neonates for potential ADE is very crucial to ensure the safety of this vulnerable population.

7. AUTHORS CONTRIBUTION STATEMENT

Dr. Meera N.K designed and supervised the study. Sara Nasrollahi gathered and analysed the data and wrote the manuscript with support from Dr. Meera N. K.

8. ACKNOWLEDGEMENT

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9. CONFLICT OF INTEREST

Conflict of interest declared none.

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