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STUDY OF DRUG PATTERN AND THEIR REGIME COMPOSITION IN THE NEONATAL INTENSIVE CARE UNIT

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ABSTRACT

Introduction: Neonates are special population. There may be major differences in the responses to drug in neonates, infant and children in comparison with adults. The aim of the present study was to investigate drug usage and their regime in the neonatal intensive care unit. **Material and Methods:** The present study was carried out in Alka neonatal intensive care unit (NICU), Department of pediatrics, Sheth V.S. General Hospital, Ahmadabad, India. The present study was conducted on 217 patients from September 2007 to February 2008. **Results:** Out of 217 patients, 69% were males and 31% were females. In this study, 43% of patients were preterm, 57% were full term. A total of 183 (84%) patients were admitted in early neonatal period. Out of 183 neonates, 134(73.2%) were admitted within first 24 hours after birth, majority 96(64.4%) were male and 72(76.5%) were preterm babies. The most frequently prescribed anti-infective systemic drugs were combination drug ampicillin and sulbactam(74.5%) followed by amikacin (70%), cefoperazone and sulbactam combination (20%), ciprofloxacin (18.5%), gentamicin (16.5%), levofloxacin (12%),cefoperazone(9.5%) and cefotaxime (7%). **Conclusion:** This study tells about morbidity pattern and its relation to gender, birth weight, and hospitalization and prescription items in neonatal ward. This study showed that premature birth and low birth weight were the main reasons for drug prescription.

KEYWORDS: Neonates, NICU, Premature Birth.

INTRODUCTION

India has a highly significant role to play in global efforts to end the preventable death of newborns and children under the age of five, given that it has the highest number of deaths among these two groups in the world.[1] Improvement in neonatal-perinatal survival is a priority health agenda in India. The current neonatal mortality rate of 20 per 1000 live births accounts for three forth of theinfant mortality in India (27 per 1000).[2]

A neonatal intensive care unit (NICU) is a highly specialized unit that provides high-quality skilled care to premature, low birth weight, or critically ill newborn. Apart from facilities for continuous clinical and biochemical monitoring and life support systems, the neonatal intensive care management involves the use of a wide range of medications with well-defined and specified therapeutic objectives.[3]

Drug therapy in hospitalized neonates and children is complex. Various factors are responsible such as pharmacokinetic and pharmacodynamics behavior of the drugs, a lack of pediatric licensed formulations and limited evidence-based dosing information for neonate and children.[4] The World health organization has estimated that half of all drugs used in NICU are prescribed or dispensed inappropriately. Critically ill neonates receive significant numbers of drugs during their hospital stay. These lead to increased patient morbidity, mortality, increased cost of therapy, and irrational use of medications.[5] When considering NICU, the importance of pediatric medication safety has been gaining increasing attention in the developed world in

the past decade. Rational use of drugs is the first priority now.[6] The principle aim of drug utilization research is to facilitate the rational use of drugs in population. Despite major advances in neonatology, there is limited information regarding current pattern of drug use in critically ill neonates in India.[3]

Hence, It was decided to conduct a drug utilization study in neonatal intensive care unit of teaching hospital to evaluate morbidity pattern, to study the prescription pattern of drugs in admitted neonatal disorders, to check appropriateness of prescribe regimes with national neonatal treatment guideline and to find the average cost of treatment.

MATERIAL AND METHODS

This prospective study was conducted in the Alka neonatal intensive care unit (NICU), pediatric department at Sheth V.S. General Hospital, Ahmadabad, India, from September 2007 to February 2008.

Patient eligibility criteria

Inclusion Criteria

- All neonate (≤ 28 days) of either sex admitted to NICU after starting date of the study.
- Guardian who could read and write either in Gujarati, Hindi or English and the Guardian who was willing to give written consent were included in this study.

Exclusion criteria

1. Patient's age more than 28 days of life and
2. Guardian who was not willing to give written consent were excluded from the study.

Ethical approval and informed consent

Institutional Ethics committee approval was obtained and written consent from patient's parents/guardian were taken before enrolment of neonates.

Data Analysis

In this study neonates who receiving at least one drug were included and data were collected on a proforma. Demographic details, gestational age, birth weight were noted at admission of neonate. Final diagnoses, length of NICU stay and outcome of treatment (survived or death or discharge against medical advice) were noted at discharge to analyze the morbidity pattern.

To evaluate the drug prescribing pattern, only one occurrence of each medication name per patient was included in the count for frequency of exposure to a medication. Various drugs and their dosage, durations, frequency, route of administration,prescription label (brand name or generic name) and costwere noted.

WHO-ATC classification system was used to categorize most frequently and less frequent prescribed drugs into various system based medicine groups. Appropriateness of prescribe drug was determined by referring to National Formulary of India (2011).

Costs were calculated in Indian Rupees paid for antimicrobial treatment, cardiovascular drugs, central nervous system drugs, locally applied drugs, analgesic syrups bills. The average cost per patient was determined by dividing total cost by number of patients admitted in NICU during the study period.

Parenteral nutrition, nutritional supplements such as calcium and vitamins, standard intravenous fluids, immunizations, oxygen, phototherapy, surfactant, blood transfusion, fresh frozen plasma and ventilation therapy were excluded in data collection and analysis. Cost of investigation and drugs which are free of cost from hospitals under government subsidy were excluded.

Statistical analysis

Collected data were entered in Microsoft Office Excel 2007 and analyzed using SPSS Inc. Statistical Software Version 16.0. Descriptive statistical analysis was done using proportion, percentages and mean ± standard deviation.

RESULTS

In this study, a total of 217 neonates admitted to Alka Neonatal Intensive Care Unit, Seth V.S. Hospital, Ahmedabad, a tertiary care hospital attached to Smt. NHL medical college were included as they had received minimum one drug during the study period.

In the present study 217 neonates were recruited, approximately two third of study population were male 149(69%), remaining 68(31%) were female. In 217 neonates, 94(43%) were preterm (born before 37 weeks) and 123(57%) were full term (born between 37-41 weeks) babies. Their mean gestational age was 34±4 weeks (range, 25-41wks). A total of 183 (84%) neonates were admitted in early neonatal period. Out of 183 neonates, 134(73.2%) were admitted within first 24 hours after birth, majority 96(64.4%) were male and 72(76.5%) were preterm babies **[Table 1]**.

The mean birth weight and length of stay for whole group were, 2050±661 g (range, 890-3680 g), and 7±5 days (range, 1-26 days) respectively. In the present study, 154 (71%) neonates were lower than 2500 g weight at the time of admission to NICU. Their birth weight wise distributions showed that 95 low birth weight (2499-1500 g), 55 very low birth weight (1000-1499 g), and 4 extremely low birth weight. Majority of these low birth weight babies were 88 (57%)preterm and 101 (65.6%) of these neonates had stayed longer than 5 days in NICU.

Common comorbid conditions for which the neonates sought admission in the NICU were Respiratory distress syndrome 29%,Neonatal infection 18.5%, neonatal jaundice 12.5%, and neonatal convulsion

4.1%,other diseases such as meconium aspiration syndrome, hypoxic ischemic encephalopathy, dermatitis, and bullous impetigo included 8%. Among these 95(61%) of neonates had associated complaint of low birth weight. Moreover, 60(28%) neonates had primary diagnosis of Low birth weight required admission in NICU **[Table 2].**

Pattern of drug use

Various systemic drug groups were used for treatment in NICU. It showed that highest number of drugs were from anti-infective for systemic use 77.9% followed by nervous system 6.7%, alimentary group and cardiovascular group 5.1% each, other system 2%. They are classify based on WHO-ATC classification system in **[Table 3].**

In this study total of 36 different medications were prescribed by physician. We observed that 77.8% drugs prescribed from national formulary of India 2011, 4th Edition.

This study reported that 19 injectable antimicrobial drugs were used for various clinical conditions **[Table 4].**Most frequently prescribed anti-infective systemic drugs were combination drug ampicillin and sulbactam(74.5%) followed by amikacin (70%), cefoperazone and sulbactam combination (20%), ciprofloxacin (18.5%), gentamicin (16.5%), levofloxacin (12%),cefoperazone(9.5%) and cefotaxime (7%).

Most often used nervous system drugs were phenobarbitone(16.5%), paracetamol, phenytoin, lorazempam, and midazolam. In alimentary system, ranitidine was administered to 18% of neonates. Cardiovascular system drugs included dopamine, dobutamine and furosemide. In respiratory drugs, aminophylline and adrenaline were used for respiratory distress syndrome.

The least frequently prescribed drugs which constitutes less than 5% in total prescription includes antibiotics like gatifloxacin, augmentin, meropenam, linezolid, vancomycin, chloramphenicol, althromycin, metronidazole, azithromycin and clavulanic acid.

Moreover, eye drops like ciprofloxacin, levofloxacin, ofloxacin, neomycin local cream, ibuprofen and phenobarbitone syrup, budesonide nasal nebulizer were prescribed.

WHO Core drug indicators

A total of 798 drugs were prescribed for 217 neonates during their hospitalization. Most common route of administration of drugs was parental route-injection 87.3% followed by local cream for skin 4.9%, eye drops 4.6%, syrup 2.4% and nasal nebulizer 0.8%. In this study the average number of drug prescribed per neonatewas 3.68. 139 (64%) neonates were administered at least 2 drugs, 55 (25%) neonates were administered more than 5 drugs concurrently for treatment.Percentage of prescription items with an antimicrobial agent were 77.9% **[Table 5].**

Antimicrobial agents were most common group of medicine administered to 202(93%) neonates during the study period. Range of antimicrobial drugs received by neonates was from 0 to 8. It is reported that 104(47.8%) neonates received minimum 3 antimicrobial drugs during their stay in hospital and among them 49% were preterm babies. The average length of hospital stay of these neonates was 11 days which was higher than whole group 7 days. **[Table 6].**

Cost of Treatment

The average total cost of medications during the hospitalization per neonates was 377.75 INR. Minimum and maximum cost of drugs was 50 INR and 4470 INR, respectively. Average cost of medication per encounter per day was 52.41 INR.

Outcome of neonate

During the study 196 (90.3%) neonates survived and discharged, it was observed that female neonate's survival rate was 100%. In this study out of 217 neonates during the study period, 8(3.7%) deaths were reported. 4 preterm babies died were diagnosed with low birth weight, respiratory distress and neonatal infection. The common risk factors associated with mortality were pre term, male baby,low birth weight, respiratory distress syndrome, neonatal infection and Rh incompatibility**[Table 7].**

Table 1: Demographic data (Sex distribution and Gestational group details).

Category		No. of neonate n=217	Early Neonatal Period (<7 days) n=183	Late Neonatal Period(7-28 days) n=34	Proportion of total neonate (%)
Sex distribution	Male	149	131	18	69
	Female	68	52	16	31
Gestational Age	Preterm(<37 weeks)	94	85	9	43
	Full Term (37-41 weeks)	123	98	25	57

Table 2: Morbidity pattern in neonatal ward.

Clinical Diagnosis	Number of times observed	Birth weight				Hospitalization days			Average no of drugs prescribed
		NW >2500G	LBW2499-1500G	VLBW1499-1000G	ELBW <1000G	<5	5-7	>7	
RDS	63	24	28	10	1	28	15	20	3.8
NI	40	10	26	4	--	14	15	11	3.3
NJ	27	10	10	5	2	14	6	7	2.8
NC	9	6	3	--	--	0	5	4	5.4
Other	18	13	4	1	--	9	4	5	3.6
LBW*	60	--	24	35	1	16	8	36	3.7
Total	217	63	95	55	4	--	--	--	--

RDS: Respiratory distress syndrome, NI: Neonatal infection, NJ: Neonatal Jaundice, NC: Neonatal convulsion, LBW: Low birth weight, NW: normal weight, VLBW: Very low birth weight, ELBW: extremely low birth weight, *Low birth weight as primary indication to admit in NICU not associated with anyother clinical condition.

Table 3: WHO-ATC drug category wise prescription distributions.

WHO-ATC Drug category	Total Prescription items 798	Percentage of total prescription
Anti-infective for systemic use	622	77.9
Nervous system	53	6.7
Cardiovascular system	41	5.1
Alimentary system	40	5.1
Respiratory system	26	3.2
Other system	16	2

WHO-ATC – world health organization Anatomical Therapeutic chemical

Table 4: Most frequently received drugs in NICU.

Name of drugs	ATC code	Number of neonate receiving (n=217)	Percentage of neonate receiving	Percentage of prescription item (n=798)
Ampicillin + Sulbactam	J01CR01	162	74.5	20.3
Amikacin	J01GB06	152	70	19
Cefoperazone + Sulbactam	J01DD62	44	20	5.5
Ciprofloxacin	J01MA02	42	19.4	5.3
Ranitidine	A02BA02	40	18.4	5
Neomycin cream	S03AA01	39	18	4.9
Phenobarbitone	N03AA02	36	16.6	4.5
Gentamicin	J01GB03	36	16.6	4.5
Levofloxacin	J01MA12	27	12	12
Dopamine	C01CA04	24	11	3
Fluconazole	J02AC01	21	9.7	2.6
Cefoperazone	J01DD12	20	9.2	2.5
Cefotaxime	J01DD01	15	6.9	1.9
Ibuprofen syrup	M01AE01	14	6.5	1.8
Dobutamine	C01CA07	13	6	1.6
Aminophylline	R03DA05	11	5.0	1.4
Piperacillin	J01CR05	10	4.6	1.3
Adrenaline	C01CA24	9	4.1	1.1
Gatifloxacin	J01MA16	6	2.8	0.8

Table 5: WHO core drug use indicators.

Indicators	Value
Total number of prescription items	798
Average number of drugs per neonate	3.68
Percentage of drugs prescribed by generic name	15%
Percentage of encounters with an antimicrobial prescribed	77.9%
Percentage of encounters with an injection prescribed	87.3%

Average days of hospital stay	7.2
Average drug cost per neonate (in INR)	377
Average drug cost per neonate per day (in INR)	52.41
Percentage of drugs prescribed from national formulary of India	77.8 %

Table 6: Antimicrobial prescription pattern.

Number of antimicrobial agent prescribed	Number of neonate received (n=217)	Preterm babies (n=94)	Hospitalization days (Average = 7.2)
0	15	2	2.4
1	5	0	2.2
2	93	41	5.5
3	43	12	6.4
4	31	22	9.8
5	16	9	12.6
>5	14	8	15.3

Table 7: Outcome of admitted Neonates.

Sr. No.	Category	Total No. of infants (n=217)	Survive n=196(90%)	Death n=8(3.6%)	DAMA * n=13 (6%)
GESTATIONAL AGE					
1	Pre term	94	84	5	5
2	Term	123	112	3	8
SEX DISTRIBUTION					
1	Male	149	132	8	9
2	Female	68	64	0	4
MORBIDITY PATTERN					
1	Respiratory distress syndrome	63	50	3	10
2	Neonatal infection	40	36	3	1
3	Neonatal jaundice	27	27	---	---
4	Neonatal Convulsion	9	9	---	---
5	Other	18	16	1	1
6	Low birth weight	60	58	1	1

* DAMA – Discharge against medical advice

DISCUSSION

This present study provides for the first time detailed overview of at drug utilization in critically ill neonates at Alka Neonatal Intensive Care Unit, Seth V.S. Hospital, Ahmedabad, a tertiary care hospital attached to Smt. NHL medical college. This 6-months sample has been used to create initial database to explorer the morbid clinical conditions, prescription pattern of medication practice, appropriateness of regimes in accordance to national formulary and to identify additional analyses needed to evaluate changes in future drug utilization study.

In present study the sex distribution of admitted neonates showed male preponderance (69%) These finding were similar to the finding of S Chatterjee et al. (62%),[7] Amin et.al (62%)[8]and Neupane et al (57%).[9] This is in contrast to Jayaram KB et al. 40%[10] A large national data set study by Clark et al.[11] and Indian national neonatal-perinatal database report 2002-03[12] reported male dominant in NICU admission. One reason is that males constituted higher live birth rate than female. And this can be reason for high male morbidity rate too. Another reason is that females have stronger immunity to fight to infection.[13]

This study demonstrated that that majority of the patient (71%) had low birth weight and more than three fourth of neonates were admitted within first 24 hours, an early neonatal period. They were male child, preterm and diagnosed with respiratory distress syndrome. These finding is very similar to Amin et al.[8] Neupane et al.[9] Chauthankar et al.[14] may be because of the fact that first week of neonatal life is extremely critical and more vulnerable for preterm and low birth weight babies. Furthermore, prematurity is major cause of low birth weight and respiratory distress syndrome these two together may be responsible for lung immaturity and difficulties in breathing adapting to external environment led to early hospitalization.[15,16]

The present study show the typical morbidity pattern which is seen in India. Respiratory problems were most common illness which brought neonates to admission in NICU. As respiratory distress syndrome was included under respiratory system, it has become the largest group responsible for morbidity condition.[17] Neonatal infections were second most common condition which sought admission in NICU. Reports from Indian study showed 50-60% of septic babies are premature babies and VLBW are more vulnerable.[18] In

our study 71% were LBW babies and 25% were VLBW.This is reflected on length of hospital stay of neonates.

This study has identified that in nearly two third of prescription items were anti-infective for systemic use (antimicrobial drugs)(77.9%). This is similar to Jayaram KB et al. 2019(60.36%).[10] and Neubert et al.[19] Brijal et al.(65.07%)[20] and Vaghela et al. (64.5%).[21] Almost ninety percentage of neonatal admission received antimicrobial treatment. A surprisingly average number of antimicrobial per prescriptions was 2.86 which is similar to Amin et al. 2.78[8] and Neupane et al. 2.44[9] Most likely reasons of higher incidence of antimicrobial use in NICU could be due to high rate of infections and lower birth rate. It could be attributed to institution policy to administer a broad spectrum antibiotic therapy to control serious infections and to lower neonatal mortality rate.[3]

Most common route of administration in neonates was parental (intravenous). This results complies with previous studies done by Chatterjee et al.[7] Amin et al[8] Neupane et al[9] Oral administration is not feasible in critically ill neonates and considering pharmacokinetic and pharmacodynamics parameter in neonates to get maximum effect and lower toxicity precise dosing by parental route is most preferred.[22]

Our data show that penicillin β-lactam antibacterial drug-ampicillin and sulbactam combination 74% and Aminoglycoside-amikacin 70%were the most common prescriptions followed by cefoperazone-sulbactam combination and floroquinolone-ciprofloxacin. These finding were similar to previously reported studies from India (S. Chatterjee et al.[7]Amin et al.[8] and Jayaram et al[10] Chauthankar et al[14]). One study reported from Nepal Neupane et al.[9] also reported same trends of prescription and a prospective drug utilization study by Neubert et al.[19] from Germany also showed that antimicrobials were most frequently prescribed drugs. As severe infections are most common cause of neonatal death in NICU, combination therapy of penicillin/cephalosporin and aminoglycoside is effective to control neonates with sepsis or suspected sepsis.[9]

A large national data set by Clark et al.[11] from US showed that ampicillin and gentamicin were commonly prescribed antibiotics. Study reported by Amin et al.[8] showed that Cefotaxime and amikacin were used as first-line therapy. In our NICU unit, ampicillin and amikacin were started as first line empirical therapy when neonates admitted in majority of cases. It can be a reason of higher incidence of neonatal exposure to these two drugs. Most common clinical conditions for antimicrobial prescription use were respiratory distress syndrome and neonatal infection. These combination will provide synergistic activity against the most common pathogen isolated in sepsis especially gram negative K.pneumonia and coagulase negative staphylococci.[23]

In this study, 77.9% drug selection and their dosage regime were in accordance to national formulary of India. Good prescribing practices were observed in our study with survival rate 90% and less duration of hospital stay. In our study an average of hospital stay per patient was 7days. However, higher number of mean hospital stay was reported by Amin et al.[8](12.07 days) and Neubert et al.[19] (19.4 days). Lower hospital stay in our study may reflect that prescribers referred to standard national guideline and selected drugs from national formulary in our NICU.

In this study, drugs were mostly prescribed by brand name. This is an alarming signal for academic hospital NICU as it increasing the cost of therapy. Hospital committee require to set a standard policy to promote the rationalization and generic prescription pattern to decrease the cost of overall medicines in pediatric department.

Finally complete analysis shows that

- Male child, preterm babies, low birth weight are major risk factors for early neonatal hospital admission, receiving higher number of drugs, and longer duration of hospital stay.
- The antibiotics are the most frequently received drugs in NICU. There are many similarity in antibiotic prescription trends from India and other countries.
- The numbers of drugs administered were inversely related to low birth weight, preterm babies, and clinical conditions such as neonatal respiratory distress, neonatal sepsis.
- Majority of prescription were proprietorname (brand name).
- Treatment selection is analogous with guideline late down by National Formerly of India.

Study Limitation

Limitation of present study were small sample size and study was conducted at single center only. Further study is required to find out broader evaluation of safety and efficacy of drug prescription in NICU. Such studies repeated at periods of time may show trends in drugs usage and changes in preferences therapies.

CONCLUSION

This drug utilization study has identified the prescription pattern of drugs in NICU of teaching hospital and discovered that antimicrobials are the most common group of medicines prescribed to neonates. This study provides an insight into morbidity pattern in neonatal ward as well as its relation to gender, birth weight, and hospitalization and prescription items. Our data suggest thatdrugs were prescribed by their brand name. Clinicians needs to be informed and trained for non-proprietary name of drugs. Another important observation from our data is that prescription practice in our NICU unit was in accordance with national neonatal guideline. Future studies need to research to

establish adequate risk-benefit profile of aminoglycoside and fluoroquinolone group in neonates. Finally, we showed that neonatal drug utilization is dynamic process and the reported use of drugs changes based on various factors.

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