$$\boxed{\text{RESEARCH BRIEF}}$$

Drug Utilization in Neonatal Intensive Care Unit of a Tertiary Care Hospital in Mumbai, India

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ABSTRACT

Objective: To study prescription pattern (using applicable WHO indicators), cost analysis and off-label use of drugs in neonatal intensive care unit of a tertiary care hospital.

Methods: The prescriptions of 460 neonates admitted to a NICU during July 2014-March 2015 were studied prospectively.

Results: Of 460 neonates, 54.8% were preterm and 73% were low birth weight (LBW). The mean (SD) prescription items per neonate were 5.7 (3.6). Overall off-label use was 12.3%, while 38% neonates received at least one off-label drug. Of 326 off-label drugs, antibiotics (69.6%) followed by non-steroid anti-inflammatory drugs (7%) were routinely used. Premature and LBW babies required more drugs with higher cost and longer stay compared to full term and normal weight babies ($P<0.01$), but the pattern of off-label use was similar across both these categories ($P>0.05$).

Conclusion: Off-label use of drugs, especially of antibiotics, is common in NICU.

Keywords: *Antibiotic, Cost analysis, Neonate, Prescriptions*.

INTRODUCTION

Evidence of safety and efficacy of drugs in adults is often extrapolated to neonates without evidence of systematic studies in neonates [1,2]. Such practices often result in ineffective drug therapy, increased use of off-label drugs, wastage of resources, increased mortality and morbidity, adverse events and cost of the treatment. We studied prescription pattern, cost and off-label use in neonatal intensive care unit (NICU) of a tertiary care hospital.

METHODS

This descriptive study was conducted in a NICU of a tertiary care hospital, Mumbai, India over a period of months (July 2014 to May 2015). Institutional Ethics Committee approval was obtained. Neonates admitted to NICU and receiving at least one drug were recruited after written informed consent from a parent/guardian. Neonates only under observation or not receiving any medications other than blood and blood products, vitamin K prophylaxis, prophylactic ophthalmic treatment, vaccines or intravenous fluids were excluded. Demographic details were noted. Various drugs prescribed, total (direct and indirect) cost, off-label use of drugs, availability of drugs on hospital schedule, duration of hospital stay and outcome of treatment (survived/dead) were noted at the time of discharge or death.

        For purpose of prescription analysis, individual drug prescribed to each neonate was considered as a 'prescription item' irrespective of total duration of its administration [3].

Off-label status of the drug was determined by referring to British National Formulary for Children (2011-2012) and Neofax (2011) whenever there was any deviation in prescribing drugs with respect to indication, dose, dosage forms, frequency of administration, and age [4,5]. Costs were calculated from patients' perspective [in Indian Rupees (INR), 1US Dollar = 62.4 INR as on 31st March 2015].   Expenses incurred due to investigations conducted outside the hospital or drugs purchased from outside and cost of travel were included in the direct cost. Loss of wages of attending parents/guardians during period of neonatal hospitalization were considered as indirect costs [6,7].

Statistical analysis: Data were analyzed using SPSS version 21. Data were expressed as Mean (SD) and/or median (range). Non-parametric data between groups were compared using Mann-Whitney test. *P* value <0.05 was considered significant.

RESULTS

Out of 1080 neonates screened, 460 were included in the study, while 620 were excluded as they received no medications and were managed by other supportive measures. Mean (SD) birth weight was 2 (0.7) kg (range 0.7 kg to 3.8 kg). Median (range) age at the time of hospitalization and length of hospital stay were 1 (1, 27) day and 10 (2, 78) days, respectively. Among neonates, 59.3% were males, 54.8% were preterm, 42.8% had low birth weight and 81.1% were from lower middle and lower socioeconomic class (modified Kuppuswami scale [8]). Common clinical conditions were respiratory distress, sepsis, pneumonia followed by meconium aspiration, neonatal seizures, and congenital heart diseases. 392 (85.2%) neonates were admitted within first few hours after birth while 421 (91.5%) were admitted during the first week of their life. 417 (90.7%) neonates survived and were discharged.

Prescription pattern analysis is described in *Table* **I**. 'Injection' was the most commonly used dosage form (61.9%) followed by drops (23.3%) and syrups (13.4%). Amikacin (35.8%), meropenem (10.1%) and dobutamine (7.7%) were most commonly prescribed generic drugs, while multivitamins (20.7%), ampicillin+sulbactam (19.9%) and calcium with phosphorus (17%) were most commonly prescribed by brand names. 41.3% of drugs were unavailable on hospital schedule and were purchased from market, of which multivitamins syrup (30.7%) was most commonly prescribed followed by calcium with phosphorus (25.2%), iron (17.9%) and caffeine (13.4%).

Of 460 neonates, 374 (81.3%) received antibiotics. Among them, 215 (57.5%) received ampicillin-sulbactam with amikacin as first-line empirical therapy, as per departmental protocol. High-end antibiotics like carbapenems, piperacillin-tazobactam, colistin, linezolid, tigecycline. were used in remaining cases (42.5%), while 18.7% of neonates did not receive any antibiotic.

Out of 2642 drugs used, 326 (12.3%) drugs were used off-label. About 175 (38%) neonates were prescribed at least one off-label drug ranging from 0-9 off-label drugs in one neonate. Most of the drugs were off-label for the 'dose' category (52%) followed by categories - 'age' (21%) and 'combined' (15%).

No drug was used off-label for 'dosage form' and 'route'. Magnesium sulphate, administered for controlling seizures in neonates, was the only drug used off-label for 'indication'. Antibiotics were most the commonly prescribed off-label class of drugs accounting for 69.6%, followed by NSAIDs (7%) and steroids (3%). Among antibiotics, meropenem (31.7%) was most commonly prescribed off-label drug followed by piperacillin-tazobactam (19.8%) and ampicillin-sulbactam (14.5%). Among NSAIDs, paracetamol, and ibuprofen and among steroids, hydrocortisone were most commonly prescribed off-label drugs, respectively. Meropenem (39%) followed by piperacillin-tazobactam (24%) were most commonly prescribed off-label drugs in 'dose' category. Ampicillin-sulbactam (18%) and colistin (43%) were most commonly used as off-label as per 'frequency' of administration and 'age', respectively. In 'combined' category, meropenem (98%) was most commonly used which was off-label for dose as well as frequency.

The average cost of hospitalization per neonate was 7383 INR (Median 4925 INR) of which direct cost was 2609 INR and indirect cost was 4774 INR. Minimum and maximum total cost of hospitalization were 60 INR and 60880 INR, respectively. Mean (SD) medical cost per neonate was 1411 (1341) INR while the average total cost of hospitalization per day was 545 INR.

Preterm (<37 weeks) and low birth weight (<2.5 kg) neonates were exposed to significantly higher number of drugs, had longer hospital stay with overall cost of treatment compared to full term neonates (P <0.05) while number and pattern of off-label drug use was similar across all neonates irrespective of gestational age and birth weight (P<0.05) (**Table** II).

DISCUSSION

In the present study, injections and antibiotics were the most common dosage form and class of drug used in neonates, respectively. Proportion of off-label use was 38%, most of them being off-label for 'dose' and antibiotics were the most common off-label class used. The number of drugs, duration of hospital stay and cost was higher in preterm and low birth weight neonates.

The study results should be interpreted in the light of following limitations. Direct costs did not consider drugs and investigations which were free of cost from hospital under government funded scheme - *Janani Shishu Suraksha Karyakram* [9]. Indirect costs did not include capital costs (buildings, medical equipment, beds) and recurrent cost (staff salary, telephone electricity and laundry bills etc), but considered costs incurred only by parents.

Prevalence of off-label use in neonates has been reported in the range of 26-62% [10-13]. In NICUs of Germany [10], Australia [11], Derby, U.K. [12], Portugal [13] and Ireland [14] at least one off-label drug was received by 70%, 80%, 90%, 69.7% and 76%, of neonates, respectively; and regulatory labels or summary of product characteristic were followed for determining off-label use. Category-wise, Carvalho, *et al.* [3] reported ampicillin as common prescribed off-label drug in 'dose' and 'frequency' category while paracetamol as off-label for 'age'. In a study by Jain, *et al.* [1] antibiotics, and anti-

epileptics were off-label in 'age' and 'dose' categories. Differences in off-label drug use reported in different studies can be attributed to differences in neonatal conditions, duration of hospitalization, availability of drugs and different resource materials (formularies/ labels) referred to determine off-label status.

Prescribing drugs by generic names and from hospital schedule is recommended to reduce the cost of treatment and thereby to promote rational use of drugs. It is usual practice to initiate antibiotic therapy without waiting for culture and sensitivity reports considering the seriousness of illness, to prevent complications due to infections and prevent nosocomial infections. Differences across NICUs regarding antibiotic use, are affected by experience of the neonatologist with respective antibiotics, local microorganism susceptibility pattern, local availability of antibiotics and underlying clinical conditions. Good prescribing practices are important in curbing antibacterial drug resistance.

Considering dearth of controlled clinical trials due to lack of interest by pharmaceutical companies and ethical issues related to neonatal recruitment, neonatologists are compelled to use drugs in an off-label manner to provide maximum benefit from available drug therapies [15]. Often prescription of off-label drugs is based on data from medical literature like case reports and series, recommendations from experts or neonatology societies [2,16]. Hence, this practice may be considered acceptable and even necessary in absence of a suitable alternative or guidelines [17]. Clinical studies are required to validate off-label use of drugs used in neonatal practice.

WHAT THIS STUDY ADDS?

- Off-label use of drugs is rampant in NICU and increased drug use and higher costs are involved in treating preterm and low birth weight neonates.

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TABLE I PRESCRIPTION PATTERN ANALYSIS (WHO/INRUD INDICATORS) OF DRUGS IN NICU

WHO INDICATORS	Results
Total number of prescription items	2642
Average number of drugs per neonate	5.7
Percentage of drugs prescribed by generic name	38.8 %
Percentage of prescriptions with antibiotics	40.8 %
Percentage of prescriptions with injections	61.9 %
Percentage of drugs prescribed from hospital schedule.	58.7%
Average number of days per hospital admission	13.5 days
Average number of drugs per inpatient-day	0.4/inpatient day
Average number of antibiotics per inpatient-day	0.2/inpatient day
Average number of injections per inpatient-day	0.3/inpatient day
Average drug cost per inpatient-day (in INR)	15/ inpatient day

WHO/INRUD- World health organization / International network for rational use of drugs, INR – Indian Rupees

TABLE II   COMPARISON OF VARIOUS VARIABLES AMONG DIFFERENT AGE AND WEIGHT
CATEGORIES

	According to gestational age on delivery			*According to birth weight*		
	Preterm	*Term*	*'P' value*	*Low birth weight*	*Normal birth weight*	*'P' value*
Total drug use	6.6 (3.8)	4.7 (3)	<0.01	6.1 (3.7)	4.8 (3.1)	<0.01
off-label drug use	0.7 (1.3)	0.6 (1.1)	0.311	0.7 (1.2)	0.6 (0.9)	0.877
Hospital stay (in days)	16.4 (13.7)	10.1 (8)	<0.01	14.9 (12.2)	9.9 (9.1)	<0.01
cost of the treatment (INR)	9069 (9294)	5341 (4752)	<0.01	7979 (8363)	5770 (5751)	0.002

Values in mean (SD; INR- Indian Rupees.