The pattern of drug use among term neonates and cost implications: Results from a study in a Sri Lankan neonatal care unit.

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key words: neonatal therapeutics, drug utilization, cost of drugs.

Abstract

Background Newborns in neonatal care units are exposed to a considerable number of medications. Although patterns of drug utilization in neonatal care units are changing rapidly, current data on drug utilization patterns in neonatal care units are limited, especially with regard to term neonates.

Objectives The aim of the study was to describe the drug utilization pattern, its associated factors and total drug cost on term neonates admitted to the Neonatal Care Unit (NCU) at Teaching Hospital Kandy (THK).

Methods and materials This study was a secondary analysis of data based on a follow-up study conducted among term neonates delivered at Teaching Hospital Kandy. A total of 175 neonates were studied over a period of 4 months, from February to May 2015.

Results Benzylpenicillin was the most frequently used drug and on average 6.16 (+2.99) drugs were prescribed per neonate. Only length of stay and sex was associated with average drug use per neonate. Nearly seventy percent of total drug cost to treat term neonates was spent on 2 drugs; gentamicin and surfactant. All the other individual drugs account for a proportion of ten percent or less.

Conclusions Being the drug which is responsible for the heights share of total drug cost, gentamicin should be monitored closely to ensure rational use. Similar studies done in large scale at regular intervals can reflect the changing patterns of drug prescribing, which helps the healthcare planners to develop necessary guidelines and take action to make necessary drugs available.

Introduction

Newborns in neonatal care units are exposed to a large number of medications. Although patterns of drug utilization in neonatal care units are changing rapidly, current data on drug utilization patterns in neonatal care units are limited, especially with regard to term neonates.^{1,2}

Newborn maturity plays a key role in determining the pharmacokinetics of a drug. This is because development factors have an effect on drug absorption, distribution, metabolism and clearance. Mean the number of drug usage is reducing with increasing gestational age as well as increasing birth weight.³

Available drug utilization patterns among newborns show that the average number of drugs administered per neonate in the neonatal intensive care unit had progressively increased over the years.³ But when focused on the term gestational age, it varies from place to place; study done in USA⁽³⁾ during 1997 to 2004, reported mean number of drug use among term neonates as 2.4, where as a study done in Germany,⁴ in 2005 reported mean number of drug use among term neonates as 10. In most of the studies, antibiotics were the drug category with the highest utilization rate.³⁻⁵

Furthermore, most of the developing countries have limited funds for health care so it is important to prescribe drugs rationally to get the maximum out of the available resources. In that case, monitoring of drug utilization pattern is important to ensure maximum utilization of purchased drugs and limit the wastage.²

Most of the reported drug utilization studies have been carried out in Neonatal Care Units (NCUs) are over-represented by preterm neonates.¹⁻⁵ So this paper is aim to evaluate the drug utilization pattern, its associated factors and total drug cost on term neonates admitted to neonatal care unit of Teaching Hospital Kandy (THK), Sri Lanka.

Methods

This study is a secondary analysis of data from a prospective follow-up study conducted among term neonates delivered at THK, to describe the drug utilization pattern and its associated factors. A total of 175 term neonates were studied over a period of 4 months from Feb to May 2015. The study was approved by the ethics review committee of the faculty of medicine Colombo.

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In the follow-up study following term neonates were excluded from the study; neonates of mothers with uncertain Last Menstrual Period (LMP), neonates of mothers who did not have an ultrasound scan (USS) before the completion of 24 weeks of gestation and neonates of mothers whose USS Expected Date of Delivery (EDD) is different from EDD calculated by the LMP more than 14 days. Since there was only one death, it was excluded from the secondary data analysis to maintain uniform survival status for the analysis. During the follow-up study, drugs prescribed to the neonates were extracted from the neonate's Bed Head Ticket. To find out the cost of drugs per each term neonate, the quantity was multiplied by the unit cost. For Drugs, which are provided by the Medical Supplies Division (MSD), the unit cost had assigned according to the annual drug estimates issued by the MSD (2015). For drugs, which are not supplied by the MSD, State Pharmaceuticals Corporation (SPC) price was used as the unit price.

All drugs were coded as per World Health Organization Anatomical Therapeutic Chemical (ATC) classification system,⁶ to describe the utilization pattern according

to the organ or system on which they act. Neonatal conditions were classified based on the main neonatal condition according to the ICD 10 classification.⁷

Categorical variables were expressed as counts (Percentages) and continuous variables as mean and median with range. Due to the skewed distribution number of drug according to the newborn characteristics were tested by using Kruskal-Wallis H nonparametric test. Data were analysed by using Microsoft Access, Excel 2016 versions and SPSS 20th version.

Results

As shown in Table 01, male neonates (66.9%) in the study sample outnumbered the female neonates. Approximately half (49.2%) of the term neonates were delivered at early term (37 or 38 weeks of gestation). Twenty-eight percent of neonates had low birth weight. Nearly half (56.6%) of the term neonates admitted to NCU was delivered through caesarean section. When considering the main diagnosis most prevalent neonatal condition was bacterial sepsis (24.0%) followed by respiratory distress of newborn (19.4%).

Table 01 Characteristics of term neonates

Newborn characteristic	Number of newborns	Percentage
Sex		
Male	117	66.9
Female	58	33.1
Gestational age at birth		
37	43	24.6
38	43	24.6
39	31	17.7
40	56	32.0
41	2	1.1
Birth weight		
<2500	49	28.0
2500-4000	121	69.1
>4000	5	2.9
Mode of delivery		
NVD	74	42.3
CS	99	56.6
Instrumental	2	1.1
Length of stay		
<= 6 days	42	24.0
7-12 Days	97	55.4
>12 days	63	36.0
Main Diagnosis according to ICD 10 classification		
P36- Bacterial sepsis of newborn	42	24.0

P22- Respiratory distress of newborn	34	19.4
P59- Neonatal jaundice from other and unspecified causes	26	14.9
P21- Birth asphyxia	17	9.7
P55- Haemolytic disease of fetus and newborn	15	8.6
P5- Slow fetal growth and fetal malnutrition	8	4.5
Z29- Need for other prophylactic measures	8	4.5
P24- Neonatal aspiration syndromes	7	4.0
P70- Transitory disorders of carbohydrate metabolism - newborn	7	4.0
P23- Congenital pneumonia	5	2.9
Q37- Cleft palate with cleft lip	2	1.1
Q3- Congenital hydrocephalus	1	0.6
Q42- Congenital absence, atresia and stenosis of large intestine	1	0.6
Q5- Spina bifida	1	0.6
Z3- Medical observation for suspected diseases and conditions	1	0.6
	175	100.0

Mean drug use was 6.16 (SD 2.99), per neonate and that was varied depending on neonatal characteristics. But, in the nonparametric analysis statistically significant associations were noted only with two factors; length

of stay and sex. Based on the birth weight the highest mean drug use was in more than 4000 g weight category, whereas according to the gestational age higher mean drug use was among 37 week babies. (Table 02)

Table 2 - Factors associated with mean drug use per term neonate

	Mean	Median	Maximum	Minimum	X ²	P
All newborns	6.16	6	22	1		
Sex					7.31	0.007
Male	6.62	6	22	1		
Female	5.24	5	12	1		
Gestational age (Weeks)					0.205	0.932
37	6.37	6	13	1		
38	6.16	6	17	1		
39	6.35	6	22	2		
40	5.91	6	14	1		
41	5.5	6	6	5		
Birth Weight (g)					3.169	0.205
<2500	6.33	6	14	3		
2500-3999	5.95	6	17	1		
>4000	9.60	6	22	5		
Mode of delivery					0.88	.644
Normal vaginal delivery	5.84	6	13	1		
Caesarean section	6.41	6	22	1		
Instrumental (Vacuum/ forceps)	5.5	6	6	5		
Length of stay (Days)						
<=6	5.14	5	13	1	24.78	0.000
6-12	5.58	6	12	1		
>12	8.92	10	22	2		

In total 38 drugs were used on term neonates. Most frequently used (10 percent or above) drugs were listed in table 03. The anti-infective, benzylpenicillin and gentamicin were the most widely used drugs followed by calcium gluconate and potassium chloride.

Table 03- Most frequently used drugs*

	Drug	Number of newborns	Percentage
1	Benzyl penicillin Injection 1 million unit vial (600mg)	169	96.6%
2	Gentamicin Sulphate Injection(20mg/2ml)	133	76.0%
3	Calcium gluconate injection	131	74.9%
4	Potassium chloride Injection	131	74.9%
5	Dobutamine Injection	36	20.6%
6	Amikacin Injection	32	18.3%
7	Cefotaxime Injection	30	17.1%
8	Morphine sulphate injection	19	10.9%
	Total number of newborns	175	
*Drugs used on more than 10 percent of newborn , except for intravenous fluid			

According to the ATC classification system, anti-infectives for systematic use (96.6%) and drugs for the blood and blood-forming organs (82.8%) have been prescribed most often, followed by drugs for alimentary tract and metabolism (74.8%). (Table 04)

Table 04 - Exposure rates (in percentage) for anatomical levels of the Anatomical Therapeutic Chemical (ACT) classification by gestational age

ATC Classification	Number of newborns	Percentage
A: Alimentary tract and metabolism	131	74.9
B: Blood and blood-forming organs	145	82.9
C : Cardiovascular system	35	20.0
H: Systemic hormonal preparations, excluding reproductive hormones and insulins	2	1.1
J: Anti-infective for systemic use	169	96.6
M: Musculoskeletal system	9	5.1
N: Nervous system	24	13.7
R: Respiratory system	7	4.0
V: Various ATC structures	1	0.6
Total number of newborns	175	

As the major group of drug prescribed on term neonates admitted to NCU, the pattern of anti-infective use was further analysed. Majority of newborns have exposed to the benzylpenicillin and gentamicin combination (56.0%) followed by benzylpenicillin and amikacin (15.4%) combination and benzylpenicillin, gentamicin and cefotaxime combination (10.9%). None of them was treated with monotherapy (Fig- 01).

Fig-01 Antibiotic prescribing pattern

When considering the total drug cost gentamicin is responsible for the greatest share of total drug cost followed by the surfactant. These two drugs shared 70 % of the total drug cost on term neonates admitted to NCU. All the other individual drugs account for a proportion of ten percent or less. (Table 05)

Table 05 - Breakdown of drug cost for term neonates

Drug Name	Unit Price (LKR)*	No of units used	Cost (LKR)	%
Gentamicin Sulphate Injection (20mg/2ml)	505.58	672	339749.76	38.4
Surfactant	25909.0	11	284999.00	32.2
Human immunoglobulin for intravenous use 1g Vial	8002.90	10	80029.00	9.0
Sodium chloride 0.18% & Dextrose 10% for intravenous infusion	86.32	352	30384.64	3.4
Linezolid Injection 600mg/300ml	7500.00	3	22500.00	2.5
Calcium gluconate injection	53.76	355	19084.80	2.1
Atracurium(IV)	56.70	312	17690.40	2.0
Morphine sulphate injection	698.53	20	13970.60	1.6
Benzyl penicillin Injection 1 million unit vial (600mg)	8.87	1247	11060.89	1.2
Albumin Solution (human)	3147.02	3	9441.06	1.1
Other			56196.31	6.3
Total cost			885106.46	100
*Based year 2015				

Discussion

Present study gave us the overall pattern of drug use in a tertiary care NCU in Sri Lanka and reflects the main neonatal conditions for which term neonates were admitted to the unit.

This type of drug utilization studies not only guides for the rational use of drugs making treatment beneficial to patients and also ensures efficient use of available funds by minimizing wastage due to purchasing of drugs which are hardly used.

Demographic profile shows male (66.9%), predominance in term neonates admitted to NCU, which is consistent with other studies done in similar settings.^{3,5,6} Neonatal sepsis was the most common neonatal condition observed in our study, followed by respiratory distress of newborn as did in most of the other published work.^{1,4,5}

In this study, the average number of drugs used per term neonate was 6.16 (± 2.99), which is less than that number reported by Neubert et al,⁴ for term neonates (10 + 8.5). Drug utilization studies in NCUs in other countries have revealed that anti-infective is the commonest group of drugs prescribed in the NCU.^{1, 3-5,8} This fits well with the findings of our analysis.

In Warrier et al³ study, ampicillin was the most frequently used anti-infective agent among term neonates followed by cefotaxime. Whereas in our study it was benzylpenicillin followed by gentamicin, which is compatible the recommendations given in the newborn

care guidelines of MOH Sri Lanka⁹, Even though guideline allows the use of ampicillin in place of benzyl penicillin. Interestingly, most of similar studies done in NCUs reported the use of ampicillin instead of benzyl penicillin. Due to the same reason, the combinations of antibiotics used in our setting was different from other settings.^{1-3,8} When considering the cost, both ampicillin and benzylpenicillin have more or less similar costs based on the unit prices.

When considering the anatomical levels of drugs used among term neonates, anti-infectives for systematic use and drugs for the blood and blood-forming organs were prescribed mostly compared to the other groups. This is in accordance with the findings of the study conducted by Neubert et al.⁴

Interestingly nearly eighty percent (79.6%) of total drug cost to treat term neonates were spent on 3 drugs; namely gentamicin, surfactant and human immunoglobulin. Being the drug which is responsible for the highest share of total drug cost, due to the relatively high unit price of paediatric preparation and high frequency of use, gentamicin should be monitored closely to ensure rational use.

If the adult formula of gentamicin 80mg/2ml ampoule (unit price LKR 7.92) was used, its total cost would be only LKR 5322.24. Even though it is a common practice, it cannot be recommended to use adult formulae instead of paediatric formulae (when it is available) as a cost saving measure, due to the higher chance of administrative errors especially in settings like NCUs.^{10,11} According to the

MSD national drug estimate report on pharmaceutical items¹² the annual requirement of paediatric formula of gentamicin sulphate Injection (20mg/2ml) was 36,215 units in the year 2016. As the most costly drug (based on the unit price) used in the setting, MOH Sri Lanka, issued a circular to ensure rational use of surfactant.¹³

Unfortunately, it was not possible to comment on the rational use of gentamicin based on the present study findings. But close monitoring of gentamicin use will help to reduce the cost by avoiding any inappropriate use if there is any. So, further studies, based on the individual case scenarios, which take appropriate use of gentamicin into account, will need to be undertaken, to explore, whether there is an inappropriate use of gentamicin in this setting and possibility of replacing gentamicin with a cheaper alternative in selected clinical situations. findings of this study we think will add to the knowledge cost of drugs they frequently used in NCU setting. This awareness will have an impact on the appropriate use of limited resources as found in other studies.¹⁴

Conclusion

Benzylpenicillin was the most frequently used drug and on average 6.16 (+2.99) drugs were prescribed per term neonate admitted to NCU in TH Kandy. Nearly eighty percent of total drug cost to treat term neonates was spent on 3 drugs. Being the drug which is responsible for the heights share of total drug cost, gentamicin should be monitored closely to ensure rational use. Similar studies done in large scale at regular intervals can reflect the changing patterns of drug prescribing, which helps the healthcare planners to develop necessary guidelines and take action to make necessary drugs available.

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