

Off Label Prescribing in Neonatal Intensive Care Unit: A Prospective Observational Study

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Received: 29-11-2022 / Revised: 30-12-2022 / Accepted: 30-01-2023

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Conflict of interest: Nil

Abstract

Background: Hospitalized newborns need multiple medications to survive and in most situations, therapeutic options might get restricted without off-label prescribing of medicines. This study was planned to evaluate the off-label and unlicensed use of medicines in a neonatal intensive care unit (NICU) of a tertiary care teaching hospital.

Methods: This was a 1-year prospective observational study in which prescriptions of 100 neonates who were admitted to the NICU were evaluated. For Demographic data, the patients' files were used. The drugs used were classified as off-label, unlicensed, or licensed.

Results: A total of 291 prescriptions were given to the 100 hospitalized newborns (term and preterm). The mean numbers of prescriptions and drugs received were 2.9 and 5.0, respectively for each neonate. The mean numbers of prescriptions and drugs were greater for preterm neonates. In our study, all 100 neonates received at least one drug for off-label use. Among the neonates who received off-label drugs, most of the neonates (92%) recovered at the time of discharge. In our study there was no use of unlicensed drugs and all the prescriptions had licensed drugs. Of the total 502 drugs prescribed 373(74%) were off-label and 129(26%) were prescribed on label i.e. prescribed by our reference standards. Term neonates(53.5%) were given more off-label drugs as compared to pre-term neonates(25%). Off-label prescriptions were mostly related to dose (35.9%), duration (30.5%) and frequency (30.8%). Antibiotics (mainly Ampicillin and gentamicin) were the most commonly prescribed off-label drugs.

Conclusions: Conclusions drawn from this study are that off-label drug use is very common and is a routine practice in the NICU of our setting. All the neonates were exposed to off-label drug use. There was no use of unlicensed drugs in our study. There is a need for developing proper guidelines for the use of drugs in neonates and updating the previous label of drugs for neonates through evidence-based information and clinical trials to ensure the safe and efficient use of drugs in neonates.

Keywords: Newborn, NICU, Off-label, Unlicensed, Drug use, Prescription.

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Introduction

Neonates have unique physiology due to which the pharmacokinetic findings of medicines in adults cannot be generalized to neonates. Most of the time, evidence of safety and efficacy in adults is extrapolated to neonates making their efficacy and safety in neonates questionable. [1,2] In most nations, the use of pharmaceuticals are managed by a regulatory system that divides the use of medicines into licensed and unlicensed categories.

Licensed medicines are the medicines prescribed and administered, following the terms of the marketing authorization. Unlicensed medicine refers to the use of medicine in the following circumstances: the medicine is not licensed at all; licensed in another country but not in the country in which it is being used; or the medicine itself is licensed but the particular formulation being used is manufactured under a special license or extemporaneous dispensing, purchase of unlicensed formulations. [2-4]

Off-label use refers to the use of medicines outside the conditions of the product license in terms of dose, patient age, route of administration, indications, and contraindications. Off-label use should always be based on sound scientific knowledge about the medicine. [5,6]

Use of Off-label medicine in neonates is very common even in the Indian healthcare system. The incidence of off-label medicines prescribed in a neonatal intensive care unit (NICU) varies from 34% to 95.6% and the incidence of unlicensed medicines prescribed varies from 5.7% to 34.6%. [7] In a study conducted by Zheng Z *et al*, 2017, 71% of the prescriptions were off-label in nature in the pediatric intensive care unit of an Indian metropolitan city. [8] Several international organizations have emphasized that there should be pharmaceutical clinical trials with

newborns. Despite approved alternative medicine being available, there is excessive use of off-label and unlicensed medicines in neonatology.[9]

Though there is some data available on the off-label use of medicines in the pediatric age group in India but very few studies have shown off-label prescribing in the neonatal intensive care unit in India.[10] In our setup, no such study has been conducted so far. On the retrieval of literature, there are large variations in the incidence and pattern of off-label medicine prescribing in NICU due to different study designs, clinical settings, or study populations.

Keeping these facts in mind, the present study was planned to assess the use of off-label and unlicensed medicines in a neonatal intensive care unit (NICU) of a tertiary care teaching hospital. The data generated from this study will be of immense use in promoting the rational use of medicines in neonates.

Material and Methods

Study design

A prospective observational study was conducted by the Department of Pharmacology in collaboration with the Department of Paediatrics, SMGS Hospital, Government Medical College (GMC) JAMMU for a period of 1 year after getting clearance from the Institutional Ethics Committee (NO. IEC/GMC/2019/766), GMC Jammu and was carried out in accordance with Good Clinical Practice Guidelines.

Study Population

Prescriptions of 100 neonates admitted in the neonatal intensive care unit (NICU) during the study period fulfilling the required criteria of inclusion were evaluated. Neonates younger than 28 days, admitted to

the NICU for at least 24h receiving at least one medication, and whose parents or legal guardians signed the informed consent form were included in the study. Neonates having incomplete records and medical records indicating only the use of oxygen therapy, vaccines, vitamins, total parenteral nutrition, and intravenous hydration were excluded from the study.

Patient's data: From the medical records of neonates, we collected information about the patient's age, weight, sex, duration of stay, gestational age (GA), the primary reason for hospitalization, and diagnosis.

Neonates were divided into two groups: A. Based on their GA: 1. Preterm neonates: < 37 weeks GA, which itself consisted of 2 subgroups: < 32 weeks GA, 32-36 weeks GA. 2. Term neonates: \geq 37 weeks GA. B. Based on their birth weight: Very low birth weight (<1500g), Low birth weight (<2500g), and Normal birth weight (\geq 2500g)

Categorization of medicines

Details of all the medicines given during NICU stay of neonates such as the number of medicines, names, the medicine categories, the doses, the routes of administration, the dosage forms, indications, the duration and the frequency of administration of the medicines, were collected. Medicines were classified according to the Anatomical Therapeutic Chemical Classification (ATC). Medicines were categorized according to Food and Medicine Administration (FDA) approval criteria. Medicines were classified into three categories: licensed, off-label, and unlicensed. The categorization of medicines in terms of licensed, off-label, and unlicensed is derived from Cloherty and Stark's Manual of Neonatal Care, Nelson –Textbook of pediatric 21st edition, national formulary of India 2016, British national formulary for children 2016-2017. Off-label medicines prescribed in NICU were classified as off-

label for age, dose, duration, frequency, route, and indication.

Medicine was categorized as off-label for an age when there was no information available regarding its administration in neonates or preterm neonates, or the medicine was approved for administration in a different age group. When a medicine is categorized off-label for age, it was not further assessed for other off-label categories.

A medicine was considered off-label for dose in cases where the medicine information was available, but the administration is recommended for a higher or lower dose. In the cases where the medicine information suggested the administration of the medicine for another dosing interval, route of administration, or indication, the medicine was classified as off-label in terms of a dosing interval, route of administration, or indication.

Statistical Analysis

Data was analyzed with the help of computer software MS Excel and SPSS version 17. Mean, standard deviation (for quantitative variables), frequency, and percentage (for qualitative variables) were used for describing data.

Descriptive statistics were used for depicting demographic and clinical data, the total number of off-label medicines used, the number of medicines used, and reasons for off-label use as a number, percentage, mean, and standard deviation. Off-label medicine use was reported as a proportion along with a corresponding 95% confidence interval.

Results

A total of 100 neonates who were hospitalized in NICU for at least 24 h in the department of pediatrics and had complete clinical records were included in this study for analysis. There were male preponderances in our study (75%). The mean

gestational was 36.02 weeks. The majority of the neonates were under the age of 7 days (82%) with a mean age of 4.89 days. Of all neonates, 62% of neonates have a birth weight ≥ 2000 g, mean birth weight was 2341.45 ± 741.75 g.

The mean number of hospitalization days was 15.4 ± 10.54 . Out of all neonates, 92% of neonates recovered, 2% were referred and 6% died at the time of discharge. (Table 1) The most common admission diagnosis was respiratory distress syndrome, followed by prematurity, sepsis, Neurological illness, and Birth asphyxia (Figure 1)

A total of 291 prescriptions (2.9 ± 2.34), were given to neonates. The neonates have been prescribed an average of 5.02 ± 3.16 medicines with a minimum of medicines prescribed two and a maximum of fifteen. In our study, 502 medicines were prescribed out of which 74% were off-label and 26% were on-label i.e. prescribed in accordance with our reference standards (Figure 2).

Of the 100 neonates, all neonates received at least one medicine for off-label use. In our study, there was no use of unlicensed medicines and 100% of prescriptions had licensed medicines. Very preterm neonates were prescribed more medicines than term neonates and moderately preterm neonates. Term neonates were given more off-label prescriptions (58%) as compared to moderately preterm (25%) and very preterm (17%). (Table 2)

According to the Anatomical therapeutic chemical classification, the highest number

of off-label medicine used was Group J (Anti-infectives for systemic use) with approximately 97% of all the medicines in this prescribed off-label followed by Group N (Nervous system) and Others (Figure 3).

Ampicillin (23.8%) was the commonly prescribed off-label medicine followed by gentamicin (19.2%), cefotaxime (18.9%), and amikacin (10.5%). The less commonly prescribed off-label medicines were caffeine citrate (0.6%), vitamin K (0.6%), and ranitidine (0.6%) (Table 3)

A medicine can be classified as off-label due to various reasons such as off-label for age, dose, duration, frequency, indication, and route of administration. In our study, medicines classified as off-label were in terms of dose (35.9%), duration (30.5%), and frequency (30.8%) followed by indication (2.1%), age (0.3%), and route of administration (0.3%). Each medicine prescribed off-label can have one or more than one reasons for being classified as off-label. As such ampicillin, cefotaxime, gentamicin, amikacin, netilmicin, meropenem, and vancomycin, were off-label for dose/frequency/duration, fluconazole for dose/frequency/duration/indication, linezolid for dose/frequency, colistin and cloxacillin-ciprofloxacin for age, piperacillin-tazobactam combination for dose/frequency/duration, caffeine citrate for dose, vitamin K for the route of administration, ranitidine for dose/indication, phenobarbitone for frequency, and midazolam for dose. (Table 4, Table 5)

Table 1: Demographic and clinical data of neonates admitted to NICU, n = 100.

Variable	N	(%)
Sex		
Male	75	75%
Female	25	25%
Gestational age		
<32 weeks	17	17%
≥ 32 weeks and <37 weeks	25	25%

≥37 weeks	58	58%
MEAN Gestational age	36.02±3.63	
Age (days)		
<7 days	82	82%
>7 days	18	18%
Mean age	4.89	
Birth weight(gms)		
Birth weight<1500	13	13%
Birth weight≥1500 and<2000	25	25%
Birth weight≥2000	62	62%
Mean birth weight(±SD)	2341.45 ±741.75	
Type of patient		
Medical	95	95%
Surgical	5	5%
Length of stay		
<7 days	27	27%
>7 days	73	73%
Mean hospitalization length(±SD)	15.4 ±10.54	
Outcome at the time of discharge		
Recovery	92	92%
Death	6	6%
Referred	2	2%

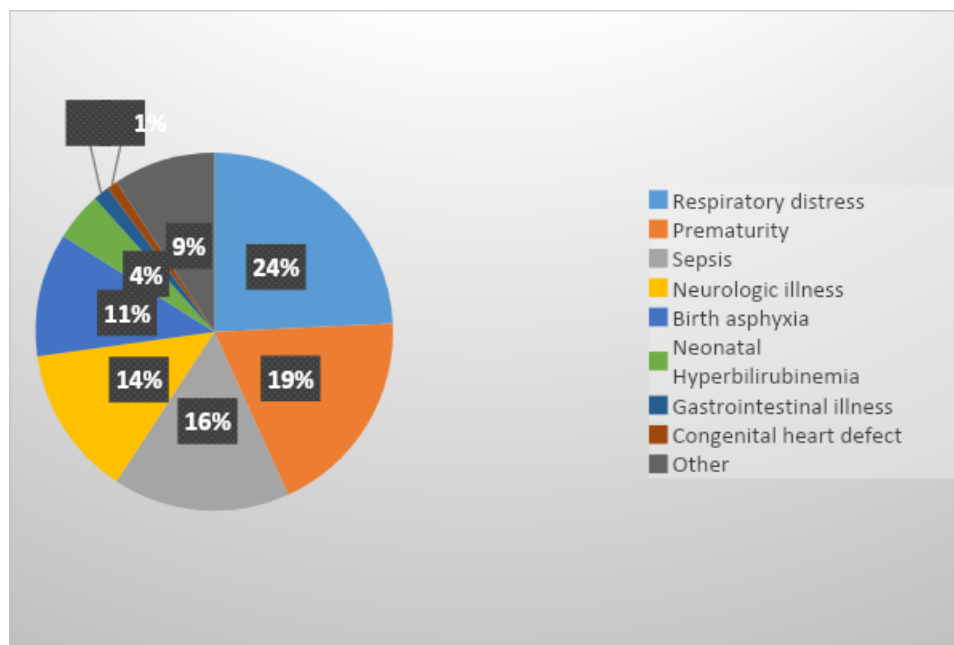
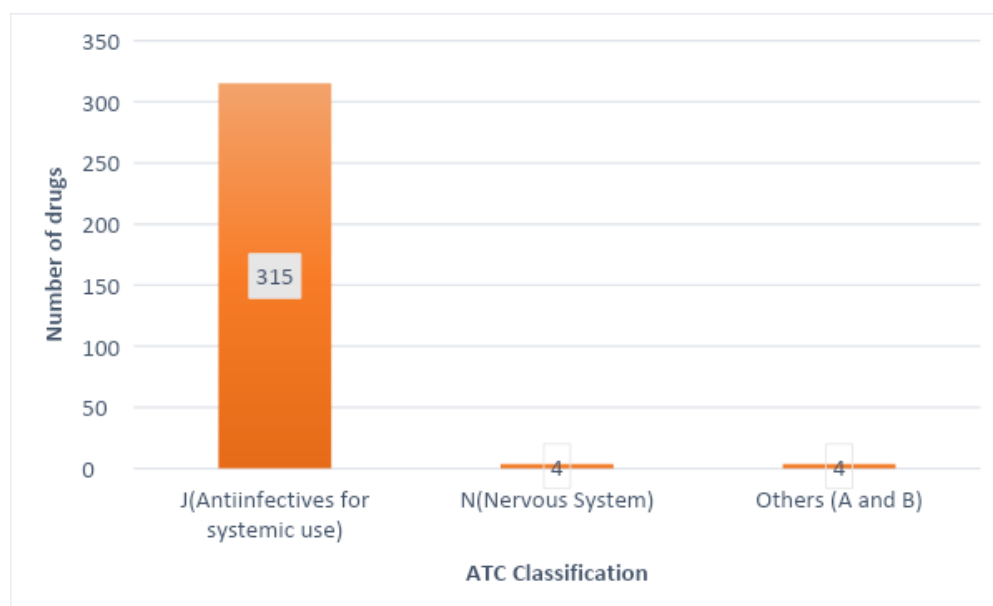


Figure 1: Primary diagnosis*

*The total of percentage didn't reach 100% because many neonates suffered from more than one diagnosis.

Table 2: Characteristics of prescriptions for neonates in NICU

Characteristics of prescriptions	Term(≥ 37 weeks)	Moderately preterm ≥ 32 and < 37 weeks	Very preterm < 32 weeks	Total neonates
Prescriptions, No Mean(\pm SD)	2.87 \pm 2.39	2.48 \pm 2.37	3.64 \pm 2.3	2.9 \pm 2.3
Drugs, Mean(\pm SD)	5.13 \pm 3.17	4.16 \pm 3.22	5.88 \pm 3.16	5.0 \pm 3.16
Off label prescriptions (%)	167(57.38)	62(21.30)	62(21.30)	291
Neonates with off label prescription, No. (%)	58(58)	25(25)	17(17)	100

**Figure 2: Frequency of off-label prescriptions by ATC (Anatomical Therapeutic Chemical) Classification****Table 3: Medicine prescribed in NICU with their off-label status and the prevalence of drugs prescribed off-label**

ATC classification	Most common medications of 502 prescribed drugs	No of medicines prescribed	Prescribed On label	Prescribed Off label	*Prevalence of medicines prescribed off label (95 %CI)
J	Ampicillin	79	2	77	23.8(19.52-28.78)
J	Gentamicin	76	14	62	19.2(15.27-23.84)
J	Cefotaxime	61	0	61	18.9(14.99-23.51)
J	Amikacin	44	10	34	10.5(7.63-14.35)
J	Meropenem	22	1	21	6.5(4.29-9.73)
J	Netilmicin	17	0	17	5.2(3.31-8.26)
J	Vancomycin	17	5	12	3.7(2.13-6.38)
J	Fluconazole	7	0	7	2.2(1.05-4.40)
J	Linezolid	7	0	7	2.2(1.05-4.40)
J	Colistin	6	0	6	1.8(0.85-3.99)

J	Cloxacillin	5	0	5	1.5(0.66-3.57)
J	Piperacillin-tazobactam combination	5	0	5	1.5(0.66-3.57)
N	Caffeine citrate	5	3	2	0.6(0.019-2.38)
B	Vitamin K	2	0	2	0.6(0.019-2.38)
A	Ranitidine	3	1	2	0.6(0.019-2.38)
N	Phenobarbitone	15	14	1	0.3(0.054-1.73)
J	Ciprofloxacin	1	0	1	0.3(0.054-1.73)
N	Midazolam	1	0	1	0.3(0.054-1.73)
	Total no. of medicine	373	50	323	

*For calculating prevalence denominator used is 323(total no. of medicine prescribed off label)

Table 4: Off-label medicine prescribed in NICU based on various reasons

Reason for off label use	%	Drugs prescribed
Dose	35.9	Ampicillin, Gentamicin, Cefotaxime, Meropenem, Amikacin, Vancomycin, Netilmicin, Fluconazole, Linezolid, Piperacillin-tazobactam combination, Ranitidine, Midazolam
Duration	30.8	Ampicillin, Gentamicin, Cefotaxime, Meropenem, Amikacin, Vancomycin, Netilmicin, Fluconazole, Piperacillin-tazobactam combination
Frequency	30.5	Ampicillin, Gentamicin, Cefotaxime, Meropenem, Amikacin, Vancomycin, Netilmicin, Fluconazole, Linezolid, Piperacillin-tazobactam combination, Phenobarbitone
Age	2.1	Colistin, Cloxacillin, Ciprofloxacin
Indication	0.3	Fluconazole, ranitidine
Route	0.3	Vitamin K

Table 5: The reason/combination of reasons, for off label use of medicines prescribed in NICU

Medicine	Frequency of off label use	% of the off label	Reason for off label classification
Ampicillin	77	23.8%	Dose/Frequency/Duration
Gentamicin	62	19.2%	Dose/Frequency/Duration
Cefotaxime	61	18.9%	Dose/Frequency/Duration
Amikacin	34	10.5%	Dose/Frequency/Duration
Meropenem	21	6.50%	Dose/Frequency/Duration
Vancomycin	12	3.7%	Dose/Frequency/Duration
Netilmicin	17	5.3%	Dose/Frequency/Duration
Fluconazole	7	2.2%	Dose/Frequency/Duration/Indication
Linezolid	7	2.2%	Dose/Frequency
Colistin	6	1.9%	Age
Cloxacillin	5	1.5%	Age

Piperacillin-tazobactam combination	5	1.5%	Dose/Frequency/Duration
Caffeine citrate	2	0.6%	Dose
Vitamin K	2	0.6%	Route of administration
Ranitidine	2	0.6%	Dose/Indication
Phenobarbitone	1	0.3%	Frequency
Ciprofloxacin	1	0.3%	Age
Midazolam	1	0.3%	Dose
Total drugs	323		

Discussion

Prescriptions of 100 neonates, admitted to the neonatal intensive care unit (NICU) during the study period were evaluated to assess the off-label prescribing of medicines. A total of 291 prescriptions were given to neonates. An average of 5.02 ± 3.16 medicines have been prescribed to neonates. Of all the medicines (502) prescribed to neonates, 74% were off-label and 26% were prescribed on-label. All neonates received at least one medicine for off-label use. Among the neonates who received off-label medicines, most of the neonates (92%) recovered at the time of discharge. In our study, there was no use of unlicensed medicines and all the prescriptions had licensed medicines. The mean gestational age of the neonates in our study was 36 weeks, which is higher than that reported in various studies.[2,11,12]. In this study, the mean hospitalization length for neonates in the NICU was 15.4 days, which was less than that reported in various studies.[7,13]

The most common cause of hospitalization for neonates in this study was respiratory distress followed by prematurity and sepsis. Similar findings have been observed in previous studies where the most common causes of hospitalization were prematurity and respiratory distress.[4,14]

The present study evaluated that during NICU stay nearly all newborns were exposed to off-label medicines which is similar to the

result of a study done in Brazil.[7] Off-label use of medicines in NICU in our setup was higher when compared with previous literature.[11,15-18] There was no use of unlicensed prescriptions in the present study, however on retrieval of literature, most of the studies done in the past have shown some use of unlicensed prescriptions. [19-21] The differences in the results of various studies could be due to different methods used, and different definitions used for off-label and unlicensed medicines.

Systemic antibiotics were the most commonly prescribed off-label medicines in neonates followed by nervous system medicines and others. Similar findings are observed in many other studies.[22,23] Ampicillin (24%) and Gentamicin (19%) were the most commonly prescribed off-label antibiotics in the present study which is similar to the findings of some of the recent studies conducted in French pediatric hospitals and Iran.[2,18] Frequent use of antibiotics can be justified as most of the neonates in NICU suffered from respiratory distress syndrome, prematurity, and sepsis. Some infections in the neonate can even present with nonspecific signs and symptoms and there is a need of immediate treatment with broad-spectrum empiric antibiotics while waiting for the laboratory results or further information to improve the clinical status of the neonate and to save the

neonate.[24] Antibiotics should be changed according to the laboratory findings or stopped in case of negative cultures. There is a need for proper monitoring of the use of antibiotics according to in-hospital or national guidelines. The selection of antibiotics depends on the experience of the different physicians, and on the antibiotic policy of each hospital [18]. The considerable amount of antibiotic misuse in the pediatric population is one of the most important global public health issues. Misuse of antibiotics can lead to the development of antibacterial resistance, increasing costs of health services, and the development of side effects such as gastrointestinal side effects.[25]

Besides antibiotics, Caffeine citrate was used off-label in terms of dose but not for indication. Earlier theophylline was more prescribed than caffeine citrate but later on, it has been seen that the use of caffeine is better than the use of theophylline due to fewer side effects and a broader therapeutic index. In 2009, caffeine became licensed for the treatment of apnea in neonates. Licensing of caffeine citrate suggests that the label does not automatically mean that the best evidence is already given and in fact, there can be a change in the label of medicine from off-label to on-label and from on-label to off-label according to the best evidence available.[21]

off-label use of medicines can be in terms of dose, duration, frequency, patient's age, route of administration, and indication. In this study, the most common off-label medicine prescribed was related to dose (35.9%), duration (30.5%), and frequency (30.8%). The dose and frequency were the commonest reasons for off-label prescription in many studies.[14,26] However, the findings of some studies were different from those of the present study which revealed that 75% of prescriptions were off-label for age group; 26% of prescriptions were off-label

for frequency, dose, and duration, indication, route, and rate[1]

off-label categories such as dose and frequency can be easily avoided by proper and accurate selection of dose and frequency according to gestational age and weight of neonate.[14] The variation in reports of common off-label categories could be explained by differences in the definition of off-label use, differences in prescribing patterns of different settings, variations in the type of morbidities, and differences in gestational age.[19,27]

In this study, the prescription of off-label medicines was significantly higher in term neonates(53.5%) than in preterm neonates (25%). The finding of the present study is similar to those of two studies conducted in recent years.[2,19] However, among preterm neonates, off-label medicines were given to very preterm newborns (25%) than to moderately preterm neonates(21.3%). This difference can be due to the concern of the physician in treating high-risk neonates.

This study depicted that there is a high prevalence of off-label prescribing of medicines in neonates. off-label use can be avoided by providing relevant information regarding side effects and various risks of these medicines to the physicians treating neonates. Various clinical trials should be conducted to develop low-risk and suitable medicines for neonates, such as the production of oral solutions instead of tablets by pharmaceutical companies to reduce the prescription of off-label and unlicensed medicines. There is a need for an Indian neonatal formulary for neonates containing all the information needed on the clinical use of neonatal medicines in India, (like BNFC (British National Formulary for Children) in the UK).[2]. A newsletter dedicated to publishing such specific data regarding medicines likely to be used for off-label

indications would be of great help to clinicians.[28].

Limitations,

However, this study had a few limitations such as the Neonates enrolled for the study were fewer due to the COVID-19 pandemic. It was a short-duration study. Further studies are needed to generalize the findings about the prescription of off-label and/or unlicensed medicines cannot be generalized to the whole country. We could not comment on the safety of medicines used as off-label as ADR monitoring was not done in our study.

Conclusions

Off-label use of medicine has become a routine practice in the Neonatal intensive care unit. Off-label prescription is not illegal. It can be justified when there is no alternative treatment available but it should be based on sound scientific knowledge.

This lays stress on the need for the development of proper guidelines for the use of medicines in neonates and updating the label of medicines for neonates through evidence-based information and clinical trials in India. The cooperation of pharmaceutical manufacturers, clinical pharmacologists, and clinicians is required to ensure the safe and rational use of medicines in neonates.

Abbreviations: ADR: Adverse medicine reactions; ATC: Anatomical therapeutic chemical; NICU: Neonatal Intensive Care Unit; RDS: Respiratory distress syndrome.

Acknowledgments: Authors would like to thank the department of pediatrics and the hospital staff for their cooperation during the study.

Authors Contribution Statement: Dr. Seema Gupta conceptualized and supervised the study and approved the final manuscript. Dr. Himani Gupta with the help of Dr Sunita

Pandita collected and evaluated the data and wrote the manuscript under the guidance of Dr Ashu Jamwal. In addition, Dr. Dinesh Kumar also supervised and helped with the statistics.

References

1. Jain S, Saini SS, Chawla D, Kumar P, Dhir S. Off-label use of drugs in neonatal intensive care units. *Indian Pediatr.* 2014; 51:644 –646
2. Kouti L, Aletayab M, Aletayab SMH, Hardani AK, Eslami K. Pattern and extent of off-label and unlicensed drug use in neonatal intensive care units in Iran. *BMC Paediatrics* 2019;19:1-7.
3. Choonara I. Unlicensed and off-label drug use in children: implications for safety. *Expert Opin Saf* 2004;3(2):81-83.
4. Alonso AS, Avila-Alvarez A, Eiriz MC, Roca CM, Gomez PY, Lopez AC, et al. Use of off-label drug in neonatal intensive care. *A Pediatr* 2019; 91:237-243.
5. Mir AN, Geer MI. Off-Label Use of Medicine in Children. *IJPSR* 2016;7(5):1820-1828.
6. Vadher MD, Patel K, Vadher DK, Parkar S, Raval C. Medicine utilization study of offlabel drug use in outpatient department of psychiatry: a prospective study at a tertiary care teaching hospital. *Int J Basic Clin Pharmacol* 2017; 6:581-586.
7. Costa HTMdL, Costa TX, Martins RR, Oliveira AG. Use of off-label and unlicensed medicines in neonatal intensive care. *PLOS ONE* 2018; 13(9):1-12.
8. Zheng Z, Yang M, Wu J. Ethical off-label drug use: Need for a Rethink? *Indian Paediatrics* 2017;54:447-450.
9. Veldman A, Richter E, Hacker C, Fischer D. The Use of Off-Label Medications in Newborn Infants Despite an Approved Alternative Being Available-Results of a National Survey. *Pharmacy (Basel)*. 2022;10(1):1-19.

10. Jain SS, Bavedkar SB, Gogaty NJ, Sadwareta PA. off-label drug use in children. *Indian J Pediatr.* 2008; 75:1133-1136.
11. Riou S, Plaisant F, Maucort Boulch D, Kassai B, Claris O, Nguyen KA. Unlicensed and off-label medicine use: a prospective study in French NICU. *Acta Paediatr.* 2015;104(5):228–31.
12. De Souza AS Jr, Dos Santos DB, Rey LC, Medeiros MG, Vieira MG, Coelho HLL. Off-label use and harmful potential of drugs in a NICU in Brazil: a descriptive study. *BMC Pediatr.* 2016;16:1-10.
13. Nasrollahi S, Meera NK. Prevalence of Off-label Medicine Use in Neonatal Intensive Care Unit of a Tertiary Care Teaching Hospital in India. *International Journal of Pharma and Bio Sciences*2020;11(3):18-23.
14. Kieran EA, O'callaghan N, O'donnell CP. Unlicensed and off-label drug use in an Irish neonatal intensive care unit: a prospective cohort study. *Acta Paediatr.* 2014;103(4):139-142.
15. Lindell-Osuagwu L, Korhonen M, Saano S, Helin-Tanninen M, Naaranlahti T, Kokki H. Off-label and unlicensed drug prescribing in three paediatric wards in Finland and review of the international literature. *J Clin Pharm Ther* 2009; 34:277–287.
16. Lass J, Kaar R, Jogi K, Varendi H, Metsvaht T, Lutsar I. Medicine utilisation pattern and off-label use of medicines in Estonian neonatal units. *Eur J Clin Pharmacol* 2011;67:1263–71.
17. Schweigertova J, Durisova A, Dolnikova D, Ondriasova E, Balazova M, Slezakova V, et al. Off-label and unlicensed use of medicinal products in the neonatal setting in the Slovak Republic. *Pediatr Int*2016;58:126–131.
18. Casan VA, Escribano BC, Garrido-Corro B. Off-label and unlicensed medicine drug in a Spanish neonatal intensive care unit. *Articulodeopinion.*2017;41:371–81.
19. Joret-Descout P, Prot-Labarthe S, Brion F, Bataille J, Hartmann JF, Bourdon O. Off-label and unlicensed utilisation of medicines in a French paediatric hospital. *Int J Clin Pharm.* 2015;37(6):1222-1227.
20. Cuzzolin L, Agostino R. Off-label and unlicensed drug treatments in Neonatal Intensive Care Units: An Italian multicentre study. *Eur. J. Clin. Pharmacol*2016;72:117–123.
21. Geißler C, Schulze C, Botzenhardt S, Rascher W, Neubert A. Drug Utilisation and Off-Label Use on a German Neonatal Intensive Care Unit: A Retrospective Cohort Study and 10-Year Comparison. *Pharmacy (Basel).* 2020;8(3):1-16.
22. Kumari A, Prasad PL, Satyender. Medicine utilization pattern in neonatal intensive care unit of a tertiary care hospital with particular emphasis on off-label drug use. *J Clin Neonatol* 2019;8:15-8.
23. Gidey MT, Gebretsadkan YG, Tsadik AG, Welie AG, Assefa BT. Off-label and unlicensed drug use in Ayder comprehensive specialized hospital neonatal intensive care unit. *Ital J Pediatr* 2020:1-7.
24. Johnson PJ. Pointers in practical pharmacology: antibiotic resistance in the NICU. *Neonatal. Netw.* 2012;31:109-114.
25. Salehifar E, Nasehi M, Eslami G, Sahraei S, Alizadeh Navaei R. Determination of antibiotics consumption in buali-sina paediatric hospital, sari 2010-2011. *Iranian Journal of Pharmaceutical Research* 2014;13(3):995–1001.
26. Silva J, Flor-de-Lima F, Soares H, Guimaraes H. Off-label and unlicensed drugs use in neonatology: reality in a portuguese university hospital. *Acta Med Port*2015;28(3):297–306.

27. Aamir, M., Khan, J.A., Shakeel, F, Shareef R, Shah N. Medicine utilization in neonatal setting of Pakistan: focus on unlicensed and off-label drug prescribing. BMC Pediatr 2018; 18:2-8.
28. Bavdekar SB, Gogtay NJ. Unlicensed and off- label drug use in children. J Postgrad Med 2005;51:249-252.