Original Article

# A prospective study on medication and total parenteral nutrition practices at a Neonatal Intensive Care Unit

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## ABSTRACT

**Background:** Neonates are vulnerable population and at high risk of developing drug-related problems. The extremely low birth weight (ELBW) infants require extended hospital stay in the Neonatal Intensive Care Unit (NICU). This study was aimed to evaluate the medications and total parenteral nutrition (TPN) practices at a NICU and to evaluate the clinical significance of medicine management made by the pharmacist and to assess the perception of healthcare professionals.

**Materials and Methods:** It is a prospective observational study conducted for 7 months in the NICU of a multidisciplinary advanced super specialty hospital, accredited by the National Accreditation Board for Hospitals and Healthcare. This study is approved by the Institutional Ethics Committee. A total of 51 neonates who met inclusion criteria were included in this study. Data were collected, and all statistical analyses were performed using the GraphPad Prism 6 Demo. Variables were compared with rho Spearman nonparametric correlations and paired *t*-tests.

**Results:** The present study showed that after administration of TPN, there was a significant change in the birth weight only in ELBW and very low birth weight (VLBW) neonates ($P < 0.05$). The average weight gain was more in the ELBW and VLBW groups. The study also measured the height of the preterm neonates before and after administration of TPN, and it was observed that VLBW group showed a significant increase in the height after administration of TPN ($P < 0.05$). About 0.27 cm average increase was observed from the VLBW group. Statistical analysis showed that head circumference gain after TPN administration was significant for birth weight <1000 g and 1000–1500 g neonates (*P* value 0.0192, 0.0001, respectively).

**Conclusion:** TPN and medication practices at the NICU should be highly monitored for avoiding medication errors, drug interactions, and mortality rate in neonates. The most effective method can be achieved when a clinical pharmacist become a part of it.

Key words: Adverse drug reaction, medication error, Neonatal Intensive Care Unit, neonates, total parenteral nutrition

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## INTRODUCTION

A new-born neonate is a child under 28 days of age. During these first 28 days of life, the child is at highest risk of dying. It is thus crucial that appropriate feeding and care are provided during this period, both to improve the child's chances of survival and to lay the foundations for a healthy life.[1] Preterm is defined as babies born alive before 37 weeks of pregnancy are completed.[2] There are subcategories of preterm birth, based on gestational age (GA) as extremely preterm (<28 weeks), very preterm (28–<32 weeks), and moderate to late preterm (32–<37 weeks). Neonates are particularly vulnerable population and have high chance to develop drug-related problems because of changing body size, weight-based dosages, off-labeled drug usage, availability of stock solutions in a variety of concentrations, inability to communicate with providers, and changing developmental system affecting drug absorption, distribution, metabolism, and excretion.[3] The extremely low birth weight (ELBW) infants require extended hospital stay in the Neonatal Intensive Care Unit (NICU).[4]

LBW has been defined by the World Health Organization as weight at birth of <2500 g. This is based on epidemiological observations that infants weighing <2500 g are approximately twenty times more likely to die than heavier babies. A birth weight below 2500 g contributes to a range of poor health outcomes, which is common in developing countries. There are subcategories of neonates based on birth weight as LBW <2500 g, very LBW (VLBW) <1500 g, and ELBW <1000 g.[5]

Neonates delivered at <30 weeks of gestation are born at a time of rapid brain and body growth. Sudden cessation of the placental supply of nutrients at birth makes these premature neonates susceptible to nutritional deficiencies unless enteral or parenteral nutrition (PN) is administered rapidly. In very premature neonates, enteral feeding is often given slowly, and therefore, during this period, nutrients are provided parenterally in the form of PN. Traditionally, different components of PN for neonates are prescribed individually, taking into consideration of the biochemical, nutritional, and physiological status of the neonate. Nutrition of neonates, previously often a neglected issue, has been gaining increasing importance in acute clinical management. It became clear that early nutrition in the critical period plays a crucial role in the long-term health and neurodevelopment. It is a well-known fact that at birth, preterm neonates have limited energy reserves; adequate provision of calories and protein to match intrauterine accretion rate soon after birth is required to prevent catabolic state.[6]

PN is a vital therapeutic modality for newborn, children, and adults for a number of indications used in a variety of settings. The appropriate use of this complex therapy increases clinical benefit while maximizing the potential risk for adverse events. Complications occur both because of PN admixture itself and the processes within which it is used. Many disparities exist in knowledge, skills, and PN practices, some of which can contribute to PN-related medication errors.[7] Children remain at higher risk than adults for medical errors in inpatient setting.[8]

The practice of pediatrics has always been complicated; small dose and multiple dose variations are commonplace. Manipulating doses maximize the risk of error which can adversely affect the patient outcomes. Preventable adverse drug events (ADEs) involving intravenous (IV) medications occur frequently in the ICUs. Many errors occur during medication administration; calculating infusion rates and programming pumps are high-risk steps.[9,10] Programmable infusion pumps with safety software ("smart pumps") were designed to intercept such errors by displaying alerts if continuous-infusion dosages exceed hospital-defined ranges or, for one pump, if duplicate infusions are administered.[11] Three studies indicate that the reprogramming of smart pumps in response to alerts occurs very often.[12] One study evaluated whether smart pumps prevent IV-ADEs and found no significant decrease. No studies have assessed how often preventable IV-ADEs actually match smart-pump safety features or whether expanding pump capabilities might prevent additional types of IV-ADEs.

It was estimated by the Institute of Medicine in 1999, more than 1 million injuries and almost 100,000 deaths must be attributed to medical errors annually. Most errors that occur in the prescription, dispensing, and administration of medications could have been prevented by a redesign of the systems used to deliver medications to patients. Practical interventions that attempt to change system processes, not people, were found to be most successful in the prevention of ADE.[13] Unfortunately, the underlying system failures are rarely identified and corrected.[14] Subsequently, physicians, pharmacists, and nurses are often unwitting participants in the reoccurrence of a well-known error. The rate for potential ADE is three

times higher in children than adults and substantially higher still for neonates in the NICU.

Administration of total PN (TPN), especially when prolonged, is associated with increased risk of late-onset sepsis.[15,16] Most of the bloodstream infections (BSIs) related to PN are caused by contamination of the device used for percutaneous vascular access; however, the fluid administered through the device also can become contaminated and cause BSI.[17] Various outbreaks of hospital-acquired infections have been reported through the administration of contaminated PN because of lapses in sterility during compounding PN at the hospital pharmacy.[18]

PN therapy is relatively expensive therapy, especially when personnel cost for patient monitoring, catheter care, and solution compounding are added to material cost. TPN compounding requires special, expensive equipment and infrastructure. An increasing use of TPN in relatively smaller units has created administrative and clinical challenges for hospital pharmacies. To improve the quality of life of the patient, TPN is given by central or peripheral venous access that provides micronutrients and macronutrients to meet specific nutritional requirements. It is a sterile, nutritionally balanced, and physicochemical stable solution or emulsion for IV administration.[19] TPN preparation is very expensive, technically demanding, and has several side effects.[20]

The primary objective of this study is to expand the knowledge of "Medicine Management" by reviewing medication order at the NICU, particularly to study the use of drugs, dosage forms, regimen, route, and drug interactions in the medication order, further to facilitate the preparation of TPN, and to understand the principles, characteristics, and clinical use of IV fluids used at the NICU. The secondary objective is to prevent, detect, monitor, document, and report adverse drug reactions and medication error at the NICU.

## MATERIALS AND METHODS

It is a prospective observational study conducted from January 2015 to July 2015 in a NICU of a 750-bedded multidisciplinary advanced super specialty hospital, accredited by the National Accreditation Board for Hospitals and Healthcare. This study was approved to be conducted by the Institutional Ethics Committee (Reg. No: ECR/112/inst/TN/2013). A total of 51 patients were included in this study. All the neonates admitted to the NICU and who are intended to receive TPN preparations and/or medications were included in this study. The neonates in the NICU who are not prescribed with any TPN preparation were excluded from the study. The study parameters include data such as patient demographics, types of TPN, and types of medications prescribed to them. The study parameters were collected from the patient's case reports, treatment chart, and by attending ward rounds with the physician treating the study population. All data collected during the study were statistically analyzed using GraphPad Prism 6 Demo version (La Jolla California USA); all the variables were compared with rho Spearman nonparametric correlations and paired *t*-test. To assess the statistical significance, *P* value was set at <0.05.

## RESULTS

The study categorized the neonates based on their birth weight into three types: ELBW (<1000 g), VLBW (1000–1500 g), and LBW (1500–2500 g). It was observed that a total of 51 neonates were admitted to the NICU during the study. About 13 neonates were ELBW, 26 neonates were VLBW, and 12 neonates were LBW. The present study revealed the gender-wise distribution of neonates. The demographic report showed 25% of neonates were ELBW and LBW, and 50% were VLBW. The survey clearly indicated that both genders have an equal chance for birth weight-related complications.

It was noticed that an average GA of the study population was 30 weeks. Further, it was categorized based on the birth weight. The mean GA was found to be 28 ± 3.3 weeks for ELBW neonates, 30 ± 1.6 weeks for VLBW neonates, and 33 ± 1.7 for LBW neonates. The mean GA of our study population is less. A study of the diagnosis of the included preterm neonates revealed that thirty were preterm, twenty were preterm with respiratory distress syndrome, and one was found to be omphalocele.

It was observed that ampicillin and amikacin were most commonly utilized antibiotics at the NICU ($n$ = 30). Next to antibiotic, fluconazole ($n$ = 26) was utilized. About 19 neonates were prescribed caffeine (to treat apnea of prematurity). It works by stimulating the central respiratory center and decreasing carbon dioxide threshold and increasing the response to hyperpnea. Among the study population of 51 preterm neonates, only 18 were not exposed to any antimicrobial; rest were exposed to antibiotics in

which a majority of preterm neonates were exposed to at least two antibiotics throughout the NICU.

The utilization of TPN among preterm neonates was observed. It was found that ELBW group was treated with 16 ± 8.7 days, VLBW group was 11 ± 6 days, and LBW group was 5 ± 4.2 days of TPN. This study showed that after administration of TPN, there was a significant change in the birth weight only in ELBW and VLBW neonates ($P < 0.05$). The average weight gain was more in the ELBW and VLBW groups. The height measurement of the preterm neonates before and after administrating TPN has shown that VLBW group showed a significant increase in the height with the administration of TPN ($P < 0.05$). About 0.27 cm average increase was observed from the VLBW group. Statistical analysis showed that head circumference (HC) gain after TPN administration was significant for ELBW ($P = 0.0192$) and VLBW ($P = 0.0001$) [Table 1].

From the drug interaction report, neonates treated with more than six drugs shown five drug–drug interactions as suggested by Lexicomp®. This study result shows that 33% of preterm neonates' medication order has no any medication error. Drug administration time error and TPN administration time error were observed in 12% of medication order which are prevented by the pharmacist. About 43% of neonates' medication order found with both drug and TPN administration errors [Table 2].

Pre- and post-administration impacts of TPN on serum electrolytes were monitored among preterm neonates. About 75% of preterm neonates were monitored with baseline serum electrolytes which is the first documented laboratory value. After administration of TPN, the last measure of serum electrolyte was considered as the last documented laboratory value. After administration of TPN, there was no significant difference between pre- and post-estimation of serum electrolytes ($P > 0.05$).

Spearman nonparametric correlation was performed to study the interrelationship between weight and GA, height and HC, which was observed that weight and HC has significant correlation ($P < 0.05$). ELBW and GA have a significant correlation ($P < 0.05$) [Table 3].

## DISCUSSION

The present study categorized the neonates based on their birth weight into three groups,[21] in which

**Table 1: Weight of neonate before and after total parenteral nutrition administration**

| Study group | Number of days of TPN used (mean±SD) | Weight | | | | Height | | | | HC | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Before (g) | After (g) | *P* | Average weight gain/day (g) | Before (cm) | After (cm) | *P* | Average height gain/day (cm) | Before (cm) | After (cm) | *P* | Average HC gain/day (cm) |
| ELBW | 16±8.7 | 793±157 | 1063±395 | 0.0192* | 17 | 34±3.6 | 37±4.7 | 0.0900 | 0.19 | 25±3.8 | 27±5 | 0.0192* | 0.13 |
| VLBW | 11±6.1 | 1242±158 | 1452±204 | 0.0001* | 19 | 39±5 | 42±2.8 | 0.0271* | 0.27 | 28±3.9 | 29±1.9 | 0.0001* | 0.1 |
| LBW | 5±4.2 | 1872±241 | 1832±287 | 0.194 | −8 | 41±4.5 | 44±2.9 | 0.0852 | 0.6 | 32.7±6.5 | 30.5±2.2 | 0.194$^{NS}$ | −0.4 |

*$P<0.05$, NS=Not significant, SD=Standard deviation, TPN=Total parenteral nutrition, ELBW=Extremely low birth weight, LBW=Low birth weight, VLBW=Very low birth weight, HC=Head circumference

**Table 2: Number of medication error observed during the study period**

| Birth weight | Number of preterm neonates | | | |
|---|---|---|---|---|
| | No medication error | Drug administration time error | TPN administration error | Drug and TPN administration error |
| <1000 | 0 | 3 | 1 | 8 |
| 1000-1500 | 7 | 2 | 5 | 12 |
| 1500-2500 | 10 | 1 | 0 | 2 |
| Total | 17 | 6 | 6 | 22 |

TPN=Total parenteral nutrition

**Table 3: Birth weight correlated with height, gestational age, and head circumference**

| Study group | Birth weight versus height | | Birth weight versus GA | | Birth weight versus HC | |
|---|---|---|---|---|---|---|
| | Spearman (*r*) | *P* (two-tailed) | Spearman (*r*) | *P* (two-tailed) | Spearman (*r*) | *P* (two-tailed) |
| ELBW | 0.4060 | 0.1887 | 0.6307 | 0.0312* | 0.8099 | 0.0022* |
| VLBW | 0.2395 | 0.2386 | 0.1620 | 0.4291 | 0.5348 | 0.0049* |
| LBW | 0.3510 | 0.2378 | 0.3883 | 0.1885 | 0.7684 | 0.0030* |

**P*<0.05. ELBW=Extremely low birth weight, LBW=Low birth weight, VLBW=Very low birth weight, GA=Gestational age, HC=Head circumference

the distribution of preterm neonates showed a 13 with <1000g, 26 with 1000 – 1500 g and 12 with 1500 g as their birth weight. The mean GA of our study population is 30 weeks which is less when compared to the European study (33 weeks).[21]

All the premature infants with <35 weeks of pregnancy and ill term infants should be immediately started with PN where the enteral nutrition can be replaced gradually.[22] It was reported that the administration of TPN has a significant impact on increase in the birth weight, height, and HC which is similar to the study conducted in South Africa.[23] Study data show that the requirement for TPN administration is high among the ELBW group than the VLBW and LBW groups, respectively. TPN administration is found clinically significant among the various groups. Various studies show that the administration of TPN for longer duration results in the nosocomial infections, which stresses the need to monitor the requirement for TPN administration duration to avoid any complication. Most of the infections in neonates should be treated with penicillin and aminoglycoside (vancomycin).[24] TPN administration is preferred than enteral nutrition which is 4-fold less in cost,[25] which requires the need to reduce the errors related to TPN administration; various research suggest that using computerized physician orders,[26] standardized PN[27] programmable infusion pumps[28] can avoid any medication and TPN administration error.

In addition, this study reveals that although the majority of reported medication errors do not result in harm to the NICU patient, medication errors are common in this clinical setting. The drugs commonly prescribed at the NICU were amikacin and ampicillin (antibiotics), fluconazole (antifungal), and caffeine. Various research have studied the drug utilization pattern among the neonates which is found similar with our study.[29] Among the drugs prescribed to the neonates, antibiotics were found to be used more (50%), whereas other study reports have shown that only 30% of neonatologists have prescribed antibiotics.[23] The choice of antibiotics for suspected sepsis may vary, which should be selected based on the organisms possibly involved and their susceptibility patterns.[30] This suggests the need for clinical pharmacists to be closely associated with the neonatal medicine specialists to provide a safe and effective way in prescribing medicine in the NICU.[31]

The present study evaluated the drug-drug interactions with the Lexicomp® medication database. It has shown that the increase in the number of drugs increases the chance of drug interactions. From the drug interaction report, neonates treated with more than six drugs shown five drug-drug interactions. For providing a better quality of care drug-drug interactions should be carefully studied which may improve the pharmaceutical care,[32] the number of drugs should be limited possibly in order to avoid the chances for drug-drug interactions.

Medication errors are common in pediatrics which harms the patients. Most of the manufacturer-developed medications meet the adult patients' needs. Where, in pediatrics, manipulated adult doses meet the needs of the patients. It has been shown that the more the medication is manipulated, the greater the chance for error.[33] All medication errors observed by the pharmacist during the study period were prevented through the clinical supervisor at the NICU.

## CONCLUSION

TPN is vital for the proper growth and development for preterm neonates which provides micronutrients, macronutrients, and electrolytes; thus any change or error in the calculation, preparation, and administration of TPN adversely affects the neonates, especially administration errors. Medication administration for neonates is also important because many errors occur due to frequency change in the administration of medications.

It is necessary that the provided care meets the specific health needs of patients, and the structured provision of neonatal care is to have an impact on patient outcomes. Currently, it is uncommon for clinical pharmacists in India to be a part of ward staff as seen in the USA or the UK. To maximize the benefits and minimize complications, many medical centers have developed a team approach in TPN administration. The present situation in India, physician has to take over all the roles of the entire team. We made an attempt to study the impact of clinical pharmacist services at the NICU.

Thus, TPN and medication practices at the NICU should be highly monitored for avoiding errors, drug interactions, and mortality rate in neonates. The most effective method can be achieved when a clinical pharmacist became a part of the NICU.

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### Conflicts of interest

There are no conflicts of interest.

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