*ORIGINAL*

# *Efficacy of Intravenous Fluconazole Prophylaxis on Outcomes of Very-Low-Birth-Weight Infants Admitted to the Neonatal Intensive Care Unit: A Randomized Clinical Trial*

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## Abstract

**Background:** Invasive fungal infections (IFIs) cause morbidity and mortality in very-low-birth-weight (VLBW) infants, but routine fluconazole prophylaxis remains controversial in low-prevalence units. We evaluated intravenous fluconazole prophylaxis in VLBW infants.

**Methods:** In this randomized, open-label trial, 80 infants with birth weight <1500 g and gestational age ≥25 weeks admitted to a NICU in Yazd, Iran (2020–2021) received intravenous fluconazole (3 mg/kg twice weekly for 4 weeks; n=40) or standard care (n=40). The primary outcome was IFI (positive blood culture at week 4). Secondary outcomes included respiratory morbidity, necrotizing enterocolitis, bronchopulmonary dysplasia, intraventricular hemorrhage, retinopathy of prematurity, hematological indices, length of stay, and mortality.

**Results:** IFI occurred in one fluconazole-treated infant (2.5%) versus none (0%) in controls (P=1.000); overall prevalence was 1.25% (1/80). Because only one IFI occurred, the trial was underpowered. In unadjusted analyses, the fluconazole group had higher rates of bronchopulmonary dysplasia (40% vs 17.5%, P=0.047), apnea (45% vs 20%, P=0.031), necrotizing enterocolitis (40% vs 17.5%, P=0.047), longer respiratory support (28.18 vs 19.72 days, P=0.047), and third-week neutropenia (15% vs 0%, P=0.026). However, the fluconazole group had lower gestational age (29.1 vs 30.6 weeks; P=0.0036) and birth weight (1082 vs 1222 g; P=0.0035). Adjusted GEE analyses showed no significant effect on hematological trajectories. Mortality, intraventricular hemorrhage, retinopathy of prematurity, and length of stay did not differ. No hepatotoxicity occurred.

**Conclusion:** In this low-endemicity NICU, routine fluconazole prophylaxis did not demonstrate reduced IFI, but the study was underpowered. Baseline differences may explain crude morbidity. These findings do not support prophylaxis.

**Keywords:** Fluconazole; Antifungal Agents; Very Low Birth Weight Infant; Invasive Candidiasis; Intensive Care Units

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# Background

Invasive fungal infections (IFIs), predominantly caused by *Candida* species, are devastating complications in neonatal intensive care units (NICUs), disproportionately affecting very-low-birth-weight (VLBW <1500 g) and extremely-low-birth-weight (ELBW <1000 g) infants [1-3]. The immature immune system, prolonged antibiotic exposure, central venous catheters, parenteral nutrition, and delayed enteral feeding synergistically predispose preterm neonates to fungal colonization and systemic dissemination [1-5]. Reported IFI prevalence ranges from 2% to 20% across NICUs worldwide, with ELBW infants bearing the highest burden [4-8]. Attributable mortality ranges from 11.4% to 44%, and survivors frequently suffer from severe neurodevelopmental impairment, periventricular leukomalacia, retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD) [4, 6, 9].

Fluconazole, a triazole antifungal with excellent bioavailability and a favorable safety profile, has been increasingly adopted for prophylaxis. Landmark randomized trials demonstrated significant reductions in fungal colonization and invasive candidiasis with fluconazole administration [10-12]. However, the magnitude of benefit depends critically on the baseline IFI incidence. The 2012 guideline of European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends prophylaxis when the local IFI rate exceeds 2% [13], while other authorities advocate a threshold of >15% [4, 6, 7]. This discrepancy, coupled with concerns regarding emerging fluconazole resistance, potential hepatotoxicity, and cost, has prevented universal adoption [10, 14, 15].

In Iran, data on neonatal IFI epidemiology and the impact of fluconazole prophylaxis are scarce. This study aimed to determine the efficacy of intravenous fluconazole prophylaxis on clinical outcomes of VLBW infants in the NICU of Shahid Sadoughi Hospital, Yazd, and to assess whether routine prophylaxis is justified based on local epidemiological data.

# Methods

## Study Design and Setting

This randomized, open-label, controlled clinical trial was conducted in the NICU of Shahid Sadoughi Hospital, Yazd, Iran, from June 2020 to August 2021. The study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (Ethics code: IR.SSU.MEDICINE.REC.1398.333) and complied with the Declaration of Helsinki. Written informed consent was obtained from all infant's parents or legal guardians.

## Participants

Infants were eligible if they had a birth weight <1500 g, gestational age ≥25 weeks, and a negative initial blood culture for fungus obtained on day 5 of life. Randomization occurred only after this negative culture result was available. Infants with major congenital anomalies or cyanotic heart disease were excluded. In addition to demographic and perinatal data, we prospectively recorded the presence of a peripherally inserted central catheter (PICC), exposure to systemic corticosteroids, use of third- or fourth-generation cephalosporins, carbapenems, H2-receptor antagonists, and administration of intravenous lipid emulsions. Exclusion criteria included known drug allergy, significant skin reactions, cholestasis, or any condition that would preclude follow-up (including early transfer to another hospital). No enrolled infant met these exclusion criteria or was lost to follow-up.

## Randomization and Intervention

The sample size was calculated based on the primary outcome (incidence of invasive fungal infection in previous studies in similar settings). Assuming a baseline IFI rate of 15% in the control group and a reduction to 3% in the fluconazole prophylaxis group, with a two-sided alpha error of 0.05 and a statistical power of 80%, the required sample size was estimated at 38 infants per group. To account for a potential 5% dropout rate, we aimed to enroll 40 infants in each group.

Randomization was performed using a random number table with a 1:1 allocation ratio. Allocation concealment was not formally documented. The randomization sequence was generated by the study team; the person who enrolled and assigned participants was not documented as being separate from the sequence generator. The trial was not prospectively registered in a public trial registry before enrollment; this is acknowledged as a limitation. Infants were randomly assigned 1:1 to intravenous fluconazole 3 mg/kg twice weekly for 4 weeks plus standard supportive care or standard care without antifungal prophylaxis. Baseline characteristics, including gestational age, birth weight, sex, and mode of delivery, were recorded and are reported in Table 1. Data on PICC, antenatal or postnatal corticosteroids, antibiotic exposure, parenteral nutrition, and intravenous lipid emulsions were not available for analysis.

## Outcomes

The primary outcome was the incidence of invasive fungal infection, defined as a positive blood culture for fungus at week 4. An initial screening blood culture for fungus was obtained on day 5 of life; randomization occurred only after this culture was negative. At week 4, a single 3-mL sample of peripheral venous blood was inoculated into a BACTEC™ bottle (Becton Dickinson, USA) and processed according to the manufacturer's protocol. No additional routine fungal blood cultures were obtained unless clinically indicated. Because blood culture sensitivity for fungi is volume-dependent, this low volume may have underestimated the true IFI rate. Secondary outcomes included: need for and duration of respiratory support, need for re-intubation and surfactant administration, incidence of apnea (respiratory pause >20 seconds or any duration with bradycardia/cyanosis), pneumothorax, BPD (oxygen dependence >21% at 28 days), necrotizing enterocolitis (NEC; ≥stage II), intraventricular hemorrhage (IVH; any grade by cranial ultrasound), ROP (any stage, screened at 28–36 days), treatment for ROP (intravitreal bevacizumab injection, laser photocoagulation, or both), orogastric or endotracheal bleeding, leukocytosis (>20,000/µL), neutropenia (absolute neutrophil count <1,500/µL), thrombocytopenia (platelet count <100,000/µL), hyperglycemia (blood glucose >180 mg/dL), length of hospital stay, weight at

discharge, and mortality. Laboratory assessments were performed weekly for four weeks. In the fluconazole group, liver transaminases and bilirubin were monitored to detect hepatotoxicity.

### Statistical Analysis

Data were analyzed using SPSS version 23. Categorical variables were compared using Fisher's exact test or chi-square test and are reported as n (%) with absolute risk differences and 95% confidence intervals where appropriate. Continuous variables were compared using independent T-test or Mann–Whitney U test as appropriate. Because only one primary outcome event occurred, the primary outcome comparison is descriptive and underpowered. The absolute risk difference for IFI was 2.5% (95%-CI approximately −2.3% to 7.3%). Secondary clinical outcomes were analyzed only in unadjusted comparisons; therefore, residual confounding by gestational age and birth weight cannot be excluded. For longitudinal hematological outcomes, GEE with an exchangeable correlation structure was used, including group, time, group × time interaction, and covariates for gestational age and birth weight. Secondary analyses are exploratory; no correction for multiple comparisons was applied. No enrolled infant was lost to follow-up. Missing data for some secondary variables were handled by available-case analysis; no imputation was performed. A P-value <0.05 was considered statistically significant.

## Results

### Characteristics of the Study Groups

Baseline characteristics are shown in Table 1; categorical clinical outcomes in Respiratory Outcomes

All but one infant required respiratory support; the need for support did not differ between groups. In unadjusted analyses, the mean duration of respiratory support was longer in the fluconazole group (28.18 ± 19.97 days vs. 19.72 ± 17.34 days, P=0.047). Similarly, unadjusted rates of BPD (40% vs. 17.5%, P=0.047) and apnea (45% vs. 20%, P=0.031) were higher in the prophylaxis group. No significant differences were observed in the need for re-intubation, surfactant administration, or pneumothorax.

**Table 2**; continuous clinical outcomes in Table 3; and adjusted GEE analyses in Table 4.

**Table 1.** Baseline Characteristics of the Study Groups

| Variable | Fluconazole Group (n=40) | Control Group (n=40) | P-value |
|---|---|---|---|
| Categorical | | | |
| Male gender, n (%) | 20 (50%) | 26 (65%) | 0.258 |
| Cesarean delivery, n (%) | 35 (87.5%) | 28 (70%) | 0.099 |
| Continuous | | | |
| Gestational age, weeks, mean ± SD | 29.08 ± 2.37 | 30.55 ± 1.99 | 0.0036 |
| Birth weight, grams, mean ± SD | 1082.50 ± 210.75 | 1222.25 ± 204.83 | 0.0035 |

### Fungal Infection

One infant (2.5%) in the fluconazole group developed a positive fungal blood culture at week 4, whereas no infection occurred in the control group (0%; P=1.000). The overall IFI prevalence was 1.25% (1/80). The absolute risk difference was 2.5% (95%-CI: approximately −2.3% to 7.3%). Because only one IFI occurred, the trial was underpowered to detect or exclude a clinically important effect of prophylaxis on IFI.

### Respiratory Outcomes

All but one infant required respiratory support; the need for support did not differ between groups. In unadjusted analyses, the mean duration of respiratory support was longer in the fluconazole group (28.18 ± 19.97 days vs. 19.72 ± 17.34 days, P=0.047). Similarly, unadjusted rates of BPD (40% vs. 17.5%, P=0.047) and apnea (45% vs. 20%, P=0.031) were higher in the prophylaxis group. No significant differences were observed in the need for re-intubation, surfactant administration, or pneumothorax.

**Table 2.** Categorical Clinical Outcomes of the Study Groups

| Variable | Fluconazole Group (n=40) | Control Group (n=40) | P-value |
|---|---|---|---|
| Need for re-intubation, n (%) | 13 (32.5%) | 10 (25%) | 0.622 |
| Need for surfactant, n (%) | 35 (87.5%) | 30 (75%) | 0.252 |
| Need for respiratory support, n (%) | 40 (100%) | 39 (97.5%) | 1.000 |
| Bronchopulmonary dysplasia, n (%) | 16 (40%) | 7 (17.5%) | 0.047 |
| Apnea, n (%) | 18 (45%) | 8 (20%) | 0.031 |
| Pneumothorax, n (%) | 6 (15%) | 3 (7.5%) | 0.481 |
| Necrotizing enterocolitis, n (%) | 16 (40%) | 7 (17.5%) | 0.047 |
| Intraventricular hemorrhage, n (%) | 10 (25%) | 7 (17.5%) | 0.586 |

| | | | |
|---|---|---|---|
| Retinopathy of prematurity, n (%) | 32 (80%) | 25 (62.5%) | 0.137 |
| Need for Amphotericin B, n (%) | 6 (15%) | 3 (7.5%) | 0.481 |
| Endotracheal/orogastric bleeding, n (%) | 25 (62.5%) | 16 (40%) | 0.073 |
| Positive fungal blood culture (week 4), n (%) | 1 (2.5%) | 0 (0%) | 1.000 |

**Table 3.** Continuous Clinical Outcomes

| Outcome | Fluconazole Group (Mean ± SD) | Control Group (Mean ± SD) | P-value |
|---|---|---|---|
| Length of hospital stay, days | 45.70 ± 18.02 | 38.60 ± 17.03 | 0.074 |
| Weight at discharge, grams | 1396.12 ± 344.02 | 1430.62 ± 179.31 | 0.575 |
| Duration of respiratory support, days | 28.18 ± 19.97 | 19.72 ± 17.34 | 0.047 |
| Number of re-intubations | 0.62 ± 1.18 | 0.35 ± 0.74 | 0.234 |
| Number of surfactant doses | 1.30 ± 0.88 | 1.18 ± 0.98 | 0.552 |
| Number of apnea episodes | 1.48 ± 2.26 | 0.98 ± 2.59 | 0.361 |
| IVH grade (0–4) | 0.40 ± 0.78 | 0.35 ± 0.86 | 0.786 |
| Number of bleeding episodes | 1.35 ± 1.29 | 0.80 ± 1.45 | 0.078 |

SD: Standard Deviation; IVH: Intraventricular Hemorrhage

## Gastrointestinal and Neurological Outcomes

In unadjusted analyses, NEC occurred in 16 infants (40%) in the fluconazole group versus 7 (17.5%) in the control group (P=0.047). IVH incidence (25% vs. 17.5%, P=0.586) and grade did not significantly differ. ROP was diagnosed in 80% of the fluconazole group and 62.5% of controls (P=0.137); the need for treatment (intra-vitreal injection, laser, or both) was statistically comparable.

## Hematological Parameters

In crude weekly comparisons, third-week neutropenia occurred in 6 infants (15%) in the fluconazole group versus none in the control group (P = 0.026). No other crude weekly hematological differences were statistically significant.

In the adjusted GEE analysis, fluconazole prophylaxis did not significantly affect the trajectory of hematological parameters over the 4-week study period. Although the odds of thrombocytopenia were 4.34 times higher in the fluconazole group, this difference did not reach statistical significance (P = 0.090). A significant time effect was observed for leukocytosis and thrombocytopenia, indicating that both parameters improved over time regardless of group assignment (P = 0.017 and P = 0.028, respectively). The group-by-time interactions were not significant for any parameter, suggesting that the trends over time were similar between two groups. Higher gestational age was significantly associated with increased odds of hyperglycemia (OR = 1.28 per week, 95% CI: 1.04–1.58, P = 0.019) (Table 4).

## Other Outcomes

Length of hospital stay and weight at discharge did not differ significantly between groups. Orogastric/endotracheal bleeding occurred in 62.5% of the fluconazole group and 40% of controls (P=0.073). Safety monitoring in the fluconazole group included weekly measurement of serum transaminases and total/direct bilirubin. No infant met the predefined criteria for hepatotoxicity; all transaminase and bilirubin values remained within the normal range for gestational age.

**Table 4.** Adjusted GEE Analysis of Weekly Hematological Parameters in Fluconazole vs. Control Groups

| Parameter | Effect | aOR* | 95% CI for aOR | P-value |
|---|---|---|---|---|
| Neutropenia | Group (Fluconazole vs. Control) | 2.71 | 0.44 - 16.74 | 0.283 |
| | Time (per week) | 1.14 | 0.73 - 1.76 | 0.57 |
| | Group × Time (Interaction) | 0.51 | 0.25 - 1.07 | 0.074 |
| | Gestational age (per week) | 0.92 | 0.76 - 1.11 | 0.396 |
| | Birth weight (per gram) | 1.001 | 0.999 - 1.003 | 0.265 |
| Leukocytosis | Group (Fluconazole vs. Control) | 1.82 | 0.28 - 11.90 | 0.532 |
| | Time (per week) | 0.53 | 0.32 - 0.89 | **0.017** |
| | Group × Time (Interaction) | 1.58 | 0.72 - 3.48 | 0.255 |
| | Gestational age (per week) | 0.85 | 0.65 - 1.12 | 0.252 |
| | Birth weight (per gram) | 0.99 | 0.995 - 1.002 | 0.445 |
| Thrombocytopenia | Group (Fluconazole vs. Control) | 4.34 | 0.79 - 23.8 | 0.09 |
| | Time (per week) | 0.62 | 0.40 - 0.95 | 0.028 |
| | Group × Time (Interaction) | 1.73 | 0.93 - 3.21 | 0.085 |
| | Gestational age (per week) | 1.23 | 0.92 - 1.66 | 0.168 |
| | Birth weight (per gram) | 0.99 | 0.994 - 1.001 | 0.135 |
| Hyperglycemia | Group (Fluconazole vs. Control) | 0.52 | 0.09 - 3.00 | 0.462 |
| | Time (per week) | 0.5 | 0.24 - 1.06 | 0.072 |
| | Group × Time (Interaction) | 0.61 | 0.22 - 1.66 | 0.329 |
| | Gestational age (per week) | 1.28 | 1.04 - 1.58 | **0.019** |
| | Birth weight (per gram) | 0.99 | 0.996 - 1.001 | 0.361 |

Adjusted for gestational age and birth weight. aOR = adjusted Odds Ratio. CI = Confidence Interval. Exchangeable correlation structure was used. Group reference: Control. P-values < 0.05 are shown in bold. Neutropenia: Absolute neutrophil count <1,500/µL; Leukocytosis: White blood cell count >20,000/µL; Thrombocytopenia: Platelet count <100,000/µL; Hyperglycemia: Blood glucose >180 mg/dL

# Discussion

This randomized trial found that in a NICU with very low prevalence of baseline invasive fungal infection (1.25%), routine intravenous fluconazole prophylaxis did not demonstrate a reduction in fungal infection; the only case of fungemia occurred in the fluconazole arm. Importantly, the fluconazole group had significantly lower gestational age and birth weight than the control group. Therefore, the unadjusted differences in respiratory and gastrointestinal outcomes may be explained by baseline differences rather than by fluconazole. In the adjusted GEE analysis of hematological parameters, fluconazole showed no significant independent effect on the trajectory of neutropenia, leukocytosis, thrombocytopenia, or hyperglycemia over the 4-week study period. These findings indicate that the transient third-week neutropenia observed in the crude analysis was likely an incidental finding due to multiple comparisons. Overall, the study does not demonstrate prophylactic benefit in this low-endemicity setting, but it also does not establish harm.

The overall IFI prevalence of 1.25% falls below the ESCMID-recommended threshold of 2% for initiating prophylaxis [13]. Several large, multi-center trials that established fluconazole's efficacy were conducted in units with IFI rates of 7–20% [4, 10, 12]. In low-prevalence settings, the expected absolute benefit of prophylaxis is small, and the risk–benefit balance may be less favorable than in units with higher IFI rates. Our findings are consistent with those of Lee *et al*., who reported no significant reduction in IFI or IFI-related mortality with fluconazole prophylaxis in Korean ELBW infants in a setting where IFI prevalence was similarly low [7].

The higher crude rates of BPD, apnea, and NEC observed in the fluconazole group are noteworthy, but these associations were likely driven by the significant baseline imbalance in prematurity rather than a direct drug effect. After considering the lower gestational age and birth weight in the fluconazole arm, the excess morbidity is substantially attenuated and no longer clinically compelling as a safety signal. Nevertheless, fluconazole inhibits cytochrome P450 enzymes involved in adrenal steroidogenesis [16], and in vitro data show dose-dependent reduction of cortisol production in human adrenocortical cells [17]. Relative glucocorticoid insufficiency in critically ill preterm infants could theoretically exacerbate lung inflammation, delay successful extubation, impair gastrointestinal mucosal integrity, and predispose to NEC. Reversible adrenal insufficiency attributable to fluconazole has been documented in critically ill patients [18], and azole-mediated disruption of surfactant composition has been proposed [19]. These mechanisms remain speculative and were not directly tested in our study, but they provide a biological rationale for monitoring similar endpoints in future trials.

Although the crude analysis suggested a higher incidence of third-week neutropenia in the fluconazole group, this difference was not confirmed in the adjusted GEE analysis (Table 4). While fluconazole is generally considered to have minimal myelosuppressive effects, isolated reports of neutropenia exist, particularly with prolonged courses [20]. Neutropenia is a recognized risk factor for Candida colonization and invasive disease in preterm neonates [21]; however, in this study, no clinical consequences were attributed to the transient neutropenia, and the finding is best regarded as exploratory.

Several limitations of this study must be acknowledged. Allocation concealment was not formally documented, and the randomization sequence generator and the person enrolling participants were not clearly separated. This may have introduced selection bias and may explain the baseline imbalance in gestational age and birth weight between groups. The single-center design and small sample size limit generalizability and reduce statistical power, particularly for rare outcomes and secondary analyses. Only one infant developed IFI; the study was therefore severely underpowered for the primary outcome and cannot determine whether fluconazole prophylaxis has a clinically important benefit or harm. Secondary clinical outcomes were analyzed only in unadjusted comparisons; the higher crude rates of BPD, NEC, apnea, and longer respiratory support in the fluconazole group may be due to lower gestational age and birth weight at baseline rather than to fluconazole. Because adjusted analyses for these secondary outcomes were not performed, confounding remains possible but cannot be confirmed. The open-label design may have introduced performance and detection bias, especially for clinically interpreted outcomes such as apnea, NEC staging, and BPD diagnosis, although many outcomes were based on objective criteria. Missing data for some secondary variables were handled by available-case analysis without imputation, which may reduce precision. The study was conducted during the COVID-19 pandemic, which reduced overall admissions and may have altered NICU microbial ecology and infection control practices. Blood culture sensitivity for fungi is limited in neonates, so the true IFI rate may have been underestimated. Long-term neurodevelopmental outcomes were not assessed, which limits conclusions about later safety.

Despite these limitations, the study has several strengths, including prospective randomization, weekly laboratory monitoring, and evaluation of multiple clinically relevant neonatal outcomes. It comprehensively evaluated a wide range of clinically relevant outcomes rarely reported together in a single trial, including detailed hematological monitoring and ROP treatment modalities. The pragmatic design reflects real-world decision-making in a resource-limited setting. Importantly, this is one of the first randomized trials of fluconazole prophylaxis in VLBW infants from Iran, contributing essential epidemiological data from an underrepresented region.

# Conclusion

In this single-center randomized trial conducted in a NICU with a very low observed prevalence of invasive fungal infection (1.25%), routine intravenous fluconazole prophylaxis (3 mg/kg twice weekly for 4 weeks) did not demonstrate a reduction in fungemia among

VLBW infants. However, because only one infant developed IFI, the study was underpowered and cannot exclude a clinically important benefit or harm. The crude higher rates of BPD, NEC, apnea, and longer respiratory support in the fluconazole group may be explained by baseline differences in gestational age and birth weight, but adjusted analyses for these secondary outcomes were not performed; therefore, these findings should be considered exploratory and hypothesis-generating, not evidence of harm. GEE analyses of weekly hematological parameters showed no significant independent effect of fluconazole on the trajectories of neutropenia, leukocytosis, thrombocytopenia, or hyperglycemia. No hepatotoxicity or other significant adverse events were attributable to fluconazole. These exploratory findings do not support routine fluconazole prophylaxis in settings with IFI rates below 2%, but they should not be interpreted as evidence of no effect. Unit-specific infection surveillance should guide antifungal stewardship policies, and larger, adequately powered, prospectively registered multicenter trials with allocation concealment and adjusted analyses are needed to confirm the safety and efficacy of fluconazole prophylaxis in low-endemicity settings, including long-term neurodevelopmental outcomes.

**Abbreviations**

| | |
|---|---|
| AI | Artificial Intelligence |
| aOR | adjusted Odds Ratio |
| BPD | Bronchopulmonary Dysplasia |
| CI | Confidence Interval |
| COVID-19 | Coronavirus Disease 2019 |
| ELBW | Extremely Low Birth Weight |
| ESCMID | European Society of Clinical Microbiology and Infectious Diseases |
| GEE | Generalized Estimating Equations |
| IFI / IFIs | Invasive Fungal Infection / Invasive Fungal Infections |
| IVH | Intraventricular Hemorrhage |
| NEC | Necrotizing Enterocolitis |
| NICU | Neonatal Intensive Care Unit |
| PICC | Peripherally Inserted Central Catheter |
| ROP | Retinopathy of Prematurity |
| SD | Standard Deviation |
| SPSS | Statistical Package for the Social Sciences |
| VLBW | Very Low Birth Weight |

## Declarations

**Conflict of Interest**: The authors declare no competing interests.

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**Ethics Approval and Consent to Participate**: This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (IR.SSU.MEDICINE.REC.1398.333). Written informed consent was obtained from all parents or legal guardians.

**AI Disclosure**: During the preparation of this manuscript, the authors used DeepSeek (version DeepSeek-V3) for language editing and to improve the clarity, conciseness, and overall readability of the text. The AI tool was employed solely to refine the writing; no scientific content, data analysis, or interpretation was generated by the AI. All suggestions were critically reviewed and edited by the authors, who take full responsibility for the accuracy, integrity, and originality of the content presented in this publication.

**Author Contributions**: F.S. and M.N. contributed to data collection, manuscript drafting, and project execution. S.R.M. supervised the study, contributed to study design, data interpretation, and critical revision. M.N., M.H.L., and N.N. served as advisors, contributed to clinical assessments, and reviewed the manuscript. A.D.T. conducted the statistical analyses and contributed to the interpretation of the results. All authors read and approved the final manuscript.

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