

Comparing Fluconazole and Nystatin as Antifungal Prophylactics in Very Low Birth Weight Infants: A Randomized Clinical Trial

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ABSTRACT

Objectives: Systemic fungal infections (SFIs) account for 12% of all late-onset sepsis among very low birth weight (VLBW) infants and result in adverse long-term neurodevelopmental outcomes among survivors. This study compared the prophylactic efficacies of systemic fluconazole or oral nystatin prophylaxis to prevent SFI in VLBW infants. **Methods:** In a randomized controlled clinical trial, 120 neonates with gestational age < 32 weeks and birth weight < 1500 g were randomly allocated in two groups. Patients in group A received fluconazole 3 mg/kg intravenously twice weekly from the first 72 hours of life. Patients in group B were administered oral nystatin 1 mL (100 000 units) every eight hours. The primary endpoint was SFI and its associated mortality rate during hospital stay. **Results:** The mean gestational age of the enrolled infants was 28.2 ± 1.4 weeks. Demographic characteristics were similar in both groups. SFI was detected in six (5.0%) infants with three cases from each group. Three (2.5%) patients died, two of whom were in group B. Four (6.7%) patients in group B and one (1.7%) in group A were treated for retinopathy of prematurity ($p = 0.040$). Intraventricular hemorrhage was detected in brain ultrasound examination in three (5.0%) neonates in group B and seven (11.7%) in group A ($p = 0.020$). **Conclusions:** The intravenous fluconazole and oral nystatin were similarly effective in preventing SFIs in VLBW infants. Future studies are recommended with a larger number of patients before routine administration of nystatin prophylaxis.

Among the leading causes of sepsis in very low birth weight (VLBW) infants are systemic fungal infections (SFIs). *Candida*-attributable mortality has been estimated in the range of 25–55%; survivors may experience adverse long-term neurodevelopmental outcomes.^{1–3} SFI was implicated in about 12% of all late-onset sepsis cases among VLBW infants.⁴

Mucosal and skin fungal colonization is an important risk factor for SFI. *Candida* spp. is a common colonizing organism due to its ability to adhere to the human epithelium, particularly in the gastrointestinal (GI) tract. Most infants admitted to the neonatal intensive care unit (NICU) become rapidly colonized by *Candida*; the most frequent sites during the first two weeks of life are the GI and respiratory tracts. *Candida* infection may be transmitted either from the mother during birth or as a nosocomial acquisition in the NICU.^{5,6} In addition, preterm infants' immature humoral and cell-mediated immunity, weaker immune responses,

and need for prolonged treatments, enable the growth and spread of fungal infections.

Other risk factors include the presence of central catheters, intubation, prolonged parenteral feeding, delayed enteral feeding, broad-spectrum antibiotics, and certain medications such as corticosteroids, theophylline, and histamine type 2 receptor blockers.^{4,7–9} SFI in VLBW infants is often reported from the second to sixth weeks after birth. It is not confined to hematogenous sepsis. SFI may affect the central nervous system (meningitis and brain abscesses), urinary tract, and soft and deep tissues. SFI may also cause endocarditis, endophthalmitis, hepatitis, and pneumonitis.¹⁰

Invasive fungal disease in VLBW infants can be prevented and treated by interrupting the process of colonization, for which oral nonabsorbable antifungal agents such as nystatin and intravenous fluconazole are generally used.¹¹ In cases of infection by non-albicans *Candida* species with reduced susceptibility to fluconazole, the alternative is usually

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nystatin. This study aimed to compare the efficacies of two prophylactics, systemic fluconazole, and oral nystatin, in preventing *Candida* colonization in high-risk infants.

METHODS

This randomized controlled clinical trial was conducted in Al Zahra Hospital (a tertiary referral teaching hospital in North Western Iran) from March 2020 to April 2021. The ethics committee of Tabriz University of Medical Sciences approved the study (Ref: IR.TBZMED.REC.1400.144). The study is registered in the Iranian Registry of Clinical Trials as No. IRCT20210908052412N1.

To estimate the required sample size, we used the prevalence rates reported in a Turkish study by Aydemir et al,¹² who found a *Candida* colonization rate of 11.7% in the group treated with nystatin and 10.8% in the group treated with fluconazole. Setting statistical power at 80% and significance (α) at 0.05, we arrived at a minimum required sample size of 31 in each group.

Inclusion criteria were inborn preterm infants with gestational age < 32 weeks and birth weight < 1500 g, who were managed at NICU. Exclusion criteria were major congenital anomalies, hemodynamic instability in the first two days of life,

elevated (twice the upper normal limits) levels of serum glutamic oxaloacetic transaminase and serum glutamate pyruvate transaminase in the first 72 hours of life, as well as parental refusal.

After obtaining informed written consent from parents, we enrolled 120 neonates in this study. The 'sealed envelope' method was used to randomly allocating them to two groups A and B of 60 neonates. This maintained the integrity of the random allocation process. Figure 1 shows the flow diagram of the study methodology including the selection process.

Patients in group A received 3 mg/kg fluconazole intravenously twice weekly from the first 72 hours of life which was continued for six weeks or till discharge from NICU. In cases where the intravenous line was discontinued during NICU stay, the treatment was switched to oral fluconazole 6 mg/kg twice weekly. In patients in group B, oral nystatin 100 000 unit (1 mL) was given every eight hours, from the first 72 hours of life till six weeks or discharge from NICU. The rest of the management protocols — such as respiratory management and total parenteral nutrition — were the same in both groups. The primary endpoint of the study was the comparative incidence and the associated mortality rate of SFI in each group during hospitalization. The secondary endpoint was the comparative complications of prematurity that arose in each group.

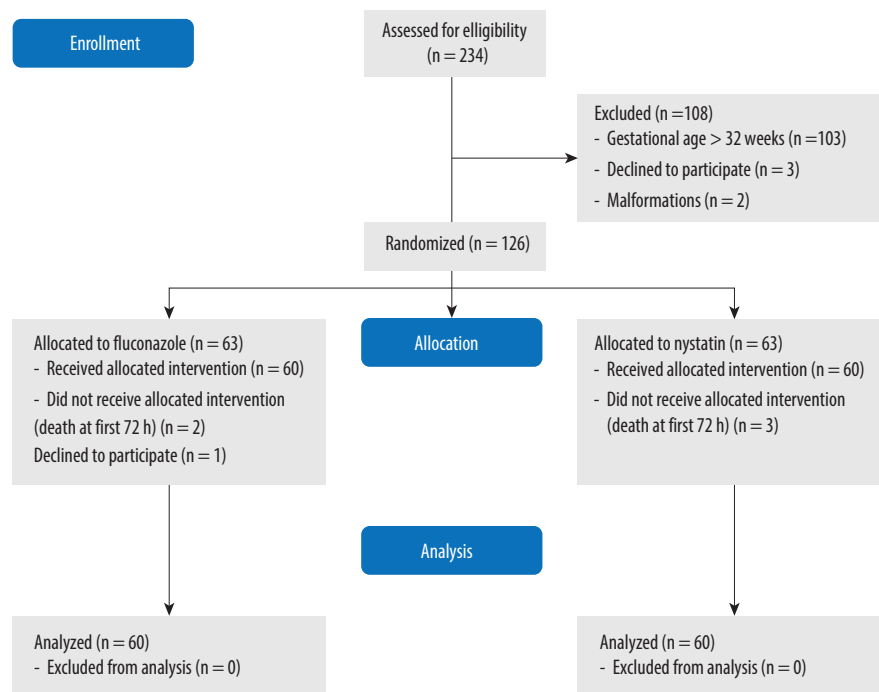


Figure 1: Flow diagram of the study methodology.

Bronchopulmonary dysplasia (BPD) was diagnosed when a preterm infant required supplemental oxygen during the initial 28 postnatal days, and it was further classified at 36-week postmenstrual age according to the degree of oxygen supplementation.¹³ Intraventricular hemorrhage (IVH) was diagnosed by cranial ultrasound examination which was performed in all infants at days 5–7 by an experienced pediatric radiologist. Retinopathy of prematurity (ROP) was diagnosed by an expert ophthalmologist by indirect ophthalmoscopic eye examination from age 4–6 weeks after birth.

Liver function tests (aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and total and direct bilirubin), complete blood count, blood urea nitrogen, and creatinine were tested weekly during the anti-fungal prophylaxis. Liver failure was defined as liver enzymes or conjugated hyperbilirubinemia > 5-fold the upper limit of normal.

All demographic, laboratory, and clinical data were recorded by an experienced nurse who was not aware of the study's objective and patient grouping.

Statistical analysis was performed using SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Quantitative data was presented as mean±SD and qualitative data as frequency and percentage. An independent *t*-test was used for testing continuous normally distributed data.

Categorical data was compared between groups using the chi-square or Fisher's exact test. Two-tailed tests were used and a *p*-value < 0.05 was considered statistically significant.

RESULTS

The subjects of this study were 120 preterm neonates (53 girls and 67 boys), the mean gestational age was 28.2±1.4 weeks. The demographic characteristics of the patients are shown in Table 1. The most common maternal complication was preeclampsia. Intubation and mechanical ventilation were performed in 18 (15.0%) neonates of whom 10 (16.7%) were from group A. The interventions and procedures in the patients are shown in Table 2.

Table 3 lists groupwise details of the SFI incidence during hospitalization. Also given are the complications of prematurity arising in each group.

Table 3 reveals that SFI was detected as fungal urinary infection in six (5.0%) infants with three cases from each group. Severe stages of ROP occurred in four (6.7%) infants in group B and one (1.7%) in group A (*p* = 0.045). Intraventricular hemorrhage was detected in brain ultrasound examination in three (5.0%) neonates in group B and seven (11.7%) in group A (*p* = 0.025). No case of necrotizing enterocolitis (NEC) or liver failure was reported in the entire cohort. Three deaths were reported overall, none of them attributable to Candida infection.

Table 1: Demographic and other characteristics of preterm infants (N = 120).

Variables	Group A (fluconazole) n = 60 n (%)	Group B (nystatin) n = 60 n (%)	<i>p</i> -value
Gestational age, weeks, mean±SD	28.4 ± 1.4	28.0 ± 1.5	0.451
Birth weight, grams, mean±SD	1169 ± 125	1145 ± 114	0.296
Male	38 (63.3)	29 (48.3)	0.141
Mean Apgar score	7.0 ± 0.7	7.1 ± 0.6	0.458
Delivery mode, cesarean section	54 (90.0)	47 (78.3)	0.089
Intrauterine growth restriction	15 (25.0)	17 (28.3)	0.394
Maternal diabetes mellitus	3 (5.0)	5 (8.3)	0.485
Preeclampsia	28 (46.7)	32 (53.3)	0.361
Prolonged rupture of membranes	4 (6.7)	3 (5.0)	0.569
Oligohydramnios	3 (5.0)	1 (1.7)	0.279
Antenatal corticosteroid			0.078
Nil	20 (33.3)	20 (33.3)	
One dose given	15 (25.0)	30 (50.0)	
Two doses given	25 (41.7)	10 (16.7)	
Maternal antibiotics	35 (58.3)	37 (61.7)	0.555

Table 2: Medical management details of preterm infants (N = 120).

Treatment	Group A (fluconazole) n = 60 n (%)	Group B (nystatin) n = 60 n (%)	p-value
Surfactant therapy	57 (95.0)	55 (91.7)	0.445
Mechanical ventilation	10 (16.7)	8 (13.3)	0.653
Peripherally inserted central catheter	26 (43.3)	25 (41.7)	0.488
Umbilical vein catheter	26 (43.3)	25 (41.7)	0.488
Intralipid	41 (68.3)	40 (66.7)	0.806
Urinary catheter	14 (23.3)	11 (18.3)	0.339
Broad-spectrum antibiotics	7 (11.7)	17 (28.3)	0.040*

*Significance.

Table 3: Primary and secondary endpoints in preterm infants (N = 120).

Endpoint	Group A (fluconazole) n = 60 n (%)	Group B (nystatin) n = 60 n (%)	p-value
Systemic fungal infection	3 (5.0)	3 (5.0)	0.999
Retinopathy of prematurity	1 (1.7)	4 (6.7)	0.045*
Intraventricular hemorrhage	7 (11.7)	3 (5.0)	0.025*
Bronchopulmonary dysplasia	12 (20.0)	20 (33.3)	0.145
Mortality	1 (1.7)	2 (3.3)	0.550

*Significance.

DISCUSSION

In our study, the rates of SFIs and mortality were similar among preterm infants with fluconazole or nystatin prophylaxis. Among the complications of prematurity, advanced stages of ROP and BPD were significantly more common in group B, whereas IVH was significantly more common in group A.

Our findings were similar to those of Aydemir et al,¹² who compared intravenous fluconazole and oral nystatin with placebo in a cohort of 278 VLBW infants. Nystatin prophylaxis resulted in decreased *Candida* colonization in the GI tract, skin, and respiratory tract. Invasive *Candida* infections were significantly lower in the fluconazole and nystatin groups compared with the placebo group (3.2%, 4.3% vs. 16.5%; $p < 0.001$). However, unlike their study, we did not have a placebo group. Several other studies, including a meta-analysis, also found nystatin to be as effective as fluconazole in preventing SFI.^{14–17}

Rundjan et al,¹⁷ compared the fungal colonization and SFI among 95 preterm infants of whom 47 received oral nystatin and 48 received placebo. The incidence of fungal colonization was 29.8% among infants in the nystatin group and 56.3% in the control group. In addition, five cases of

SFI were reported, all of which were in the placebo group. They concluded that using nystatin showed a protective effect against SFI among VLBW preterm infants without significant differences.

In our study, three (5.0%) cases developed SFI, which was less than the results of a meta-analysis that demonstrated one in every 4–9 infants receiving either fluconazole or nystatin prophylaxis was prevented from developing SFI. The lower gestational age of our cohort may explain the difference.¹⁶

No significant adverse effects have been reported in infants treated with fluconazole prophylaxis such as bacterial infections, NEC, focal bowel perforation, and cholestasis.^{18–21} Because of the very high osmolality of oral suspension of nystatin (3002 mOsm/L), there is a concern with the use of this hyperosmolar medication and the risk of NEC. Like us, Aydemir et al,¹² found no significant differences in the rates of NEC (8.6%, 9.6%, 9.9%) or mortality (8.6%, 8.5%, 12.1%) in fluconazole, nystatin, and placebo groups, respectively.

Some evidence favors fluconazole for antifungal prophylaxis owing to its greater efficacy of 80–90% compared to that of nystatin prophylaxis (50–60%), its relative safety in VLBW infants, twice-weekly

administration, intravenous administration in the case of GI disease or hemodynamic instability, and probably lower cost. Although the cost per dose of nystatin is lower, the total cost of a full course of nystatin prophylaxis, administered more than once daily, will exceed that of fluconazole, administered only twice a week.

The potential harms of routine antifungal prophylaxis include *Candida* resistance patterns, drug side effects, and cost. Limiting the prophylactic use of fluconazole to high-risk preterm infants may help delay the development of fungal resistance to antifungal drugs. Some studies recommended fluconazole prophylaxis be limited to extremely LBW (ELBW) infants, presence of central line catheters, broad-spectrum antibiotics use, and NICUs with moderate-to-high incidence of invasive candidiasis.^{19,22}

In our study, the rates of BPD and severe ROP were significantly lower in the fluconazole group than in the nystatin group. A recent Chinese study by Zhang et al,²³ compared the complications of prematurity among preterm infants treated with fluconazole prophylaxis and those with nosocomial fungal infection. They reported significantly lower BPD, ROP needing interventions, and periventricular leukomalacia/IVH in the prophylaxis group with no increased risks of serious short-term adverse side effects. A meta-analysis by Wang et al,²⁴ also found that the prophylactic use of fluconazole had no significant role in the occurrence of common complications in preterm infants.

A 2014 study found no benefit in giving antifungal prophylaxis to extremely ELBW infants, defined as weighing below 750 g.²⁵ More recently, a meta-analysis of studies on fluconazole prophylaxis in ELBW infants weighing below 1000 g found significantly decreased colonization of *Candida* spp. and lower mortality in six of the seven studies reviewed.²⁶

The limitations of this study were its small sample size, lack of long term follow-up of the studied patients, and lack of fungal colonization detection.

CONCLUSION

The oral nystatin and intravenous fluconazole were similarly effective with respect to SFI prevention in our study. Future multicenter studies with large number of patients recommended establishing the appropriate antifungal prophylaxis for best outcome. Future studies with a larger number of patients

are recommended before routine administration of nystatin prophylaxis.

Disclosure

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