Comparing the Efficacy of Systemic Fluconazole and Oral Nystatin Prophylaxis for Prevention of Systemic Fungal Infections in Very Low Birth Weight (VLBW) Infants: A Randomized Clinical Trial

Leila Asgarzadeh, Majid Mahallei and Manizheh Mostafa Gharehbaghi*

Pediatrics and Neonatology Department, Tabriz University of Medical Sciences, Tabriz, Iran

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*Corresponding address: gharehbaghimm@yahoo.com

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Abstract

Objectives: systemic fungal infections (SFI) accounts for 12% of all late onset sepsis among VLBW infants and result in adverse long-term neurodevelopmental outcomes among survivors. This study was conducted to compare the efficacy of prevention of SFI using systemic fluconazole or oral nystatin prophylaxis in high-risk infants.

Methods: in a randomized controlled clinical trial 120 neonates with gestation age less than 32 weeks and birth weight less than 1500 grams were randomly allocated in two groups. Patients in group A received 3 mg/kg fluconazole intravenously twice weekly from first 72 hours of life and patients in group B, oral nystatin 100000 unit (1 ml) was used every 8 hours. The primary outcome was systemic fungal infection during hospital stay and its mortality rate.

Results: The mean gestation age of enrolled infants was 28.26±1.45 weeks. Demographic characteristics were similar in both groups. Systemic fungal infection was detected as positive fungal urinary infection in 6 (5%) studied infants that 3 cases were each group, p= 0.99. Mortality reported in 3(2.5%) cases that was one in group A. Four (6.6%) patients in group B and one neonates (1.6%) in group A were treated for retinopathy of prematurity, p=0.04. . Intra-ventricular hemorrhage was detected in brain ultrasound examination in 3 (5%) neonates in group B and 7 (11.6%) neonates in group A, p=0.02.

Conclusion: Based on our findings, the intravenous fluconazole and oral nystatin are similarly effective with respect to SFI prevention. Future studies are recommended with large number of patients before routine administration of nystatin prophylaxis.

Keywords: candidiasis, fluconazole, nystatin, prophylaxis,, systemic fungal infection, very low birth weight infants,

Introduction

A leading cause of sepsis in very-low-birth-weight (VLBW) infants is systemic fungal infections (SFI) and result in adverse long-term neurodevelopmental outcomes among survivors. A Candida-attributable mortality estimated 25-55%.[1-3] SFI accounts for 12% of all late onset sepsis among VLBW infants.[4]

Mucosal and skin fungal colonization is an important risk factor for SFI. Candida spp. with ability to adhere to human epithelium, particularly in gastrointestinal (GI) tract is a common colonizing organism. Most infants admitted to the NICU are colonized by Candida rapidly after birth; the most frequent sites are the GI and respiratory tracts during the first two weeks of life. Maternal candida infection or neonatal nosocomial acquisition in the neonatal intensive care unit (NICU) causes colonization with Candida in neonates.[5,6] On the other hand preterm infants have

immature homoral and cell-mediated immunity, decreased immune response competency and increased need to undergo prolonged aggressive treatments that may enhance fungal growth, replication and dissemination. Other risk factors for fungal colonization and SFI are the presence of central catheters, intubation, prolonged use of parenteral nutrition, delayed enteral feeding, use of broad spectrum antibiotics, certain medications such as corticosteroids, theophylline, and histamine type 2 receptor blockers.[4,7-9] SFI in VLBW infants is often reported between the second and sixth weeks after birth. It is not confined to hematogenous sepsis. The central nervous system (meningitis and brain abscesses), urinary tract, soft and deep tissues, endocarditis, endophtalmitis, hepatitis and pneumonitis may be due to SFI.[10] In the most immature neonates, neurodevelopmental sequels and poor outcomes are not prevented by antifungal treatment.[11]

The prevention of invasive fungal disease is by interrupting the process of colonization and subsequently preventing the development of serious fungal infections. Oral non-absorbable antifungal agents suchas nystatin or intravenous fluconazole can be used for preventing colonisation.[12] There is possibility of emergence of Non-albicans Candida species with reduced susceptibility to fluconazole and also there is need to an alternative agent for antifungal prophylaxis in very low birth weight pre-term infants. The aim of this study is to compare the efficacy of prevention of candida colonization using systemic or oral non-absorbable antifungal prophylaxis in decreasing SFI among high-risk infants.

Methods

This randomized controlled clinical trial was conducted in Al Zahra hospital which is a tertiary, university referral hospital in North West of Iran from March 2020 –April 2021. Ethic committee of Tabriz University of Medical Sciences approved the study IR.TBZMED.REC.1400.144.The study registered in Iranian Registry of Clinical Trials (IRCT) by number IRCT20210908052412N1.

Considering the findings of Aydemir and coworkers study as a default and considering 11.7% candida colonization in nystatin group and 42.9% in control group with power 80% and alpha 0.05 we estimate that at least 31 cases are needed for each group.[13]

We enrolled 120 neonates in this study consisting 60 cases in each group. Before patient enrollment parental informed written consent was obtained. Exclusion criteria were major congenital anomalies, hemodynamic instability in 2 first days of life, elevated liver function tests (SGOT, SGPT) more than twice upper normal limits at first 72 hours of life and parental refuse.

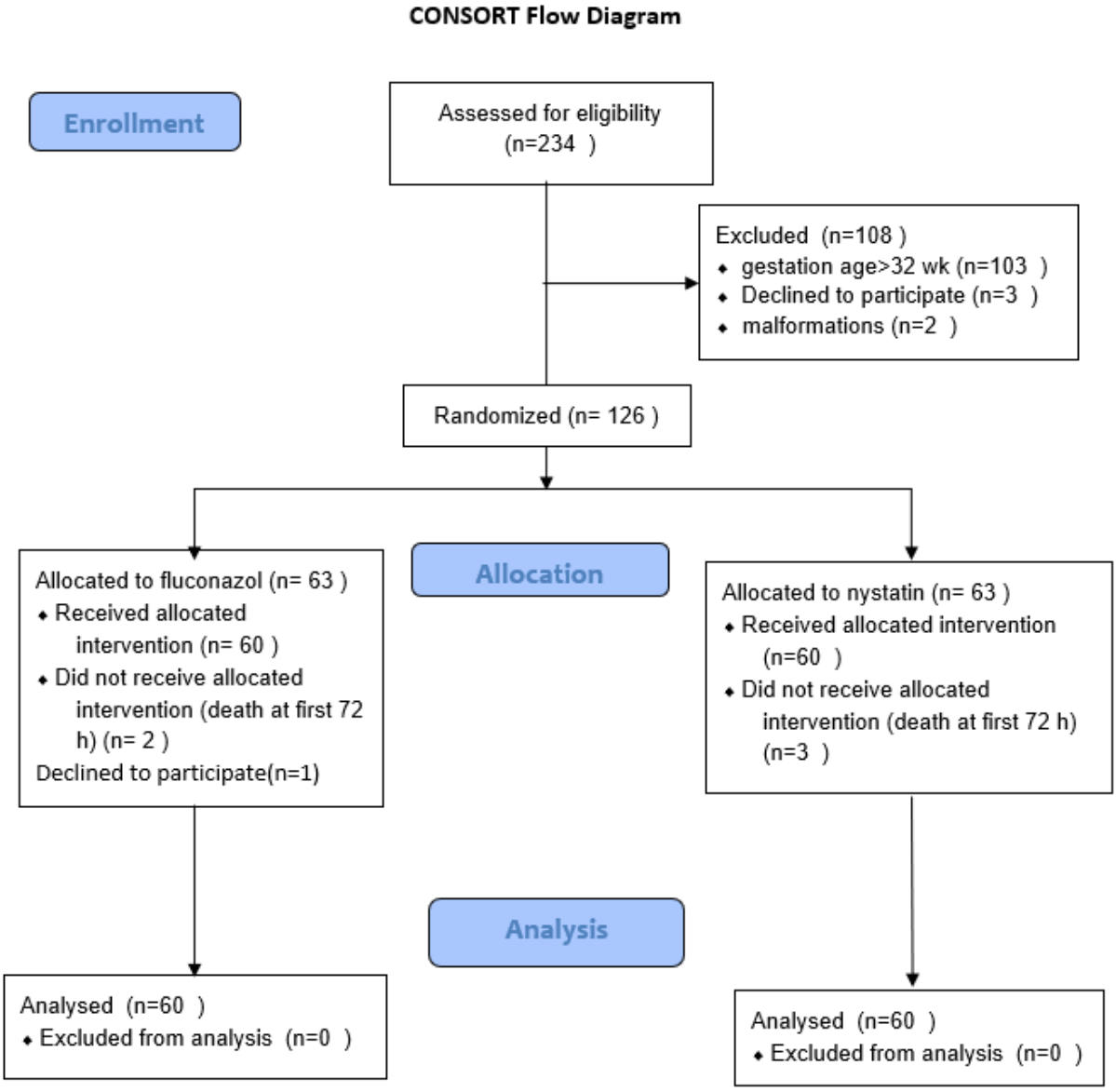
Inborn preterm infants with gestation age less than 32 weeks and birth weight less than 1500 grams were eligible for inclusion in this study. Enrolled patients were randomly allocated in two groups by random number list generated by random number generator in sealed opaque envelops. Patients in group A received 3 mg/kg fluconazole intravenously twice weekly from first 72 hours of life and continued 6 weeks or till discharge from NICU . Oral fluconazole 6 mg/kg twice weekly was replaced when IV line discontinued during NICU stay. In patients group B oral nystatin 100000 unit (1 ml) was used every 8 hours started in first 72 hours of life till 6 weeks or NICU discharge. The same protocol was used for respiratory management and total parenteral nutrition in enrolled patients of both groups. The primary outcome was systemic fungal infection during hospital stay and its mortality rate. The secondary outcome was complications of prematurity.

Bronchopulmonary dysplasia (BPD) was diagnosed when a preterm infant requires supplemental oxygen for the 1st 28 postnatal days, and it is further classified at 36 wk PMAaccording to the degree of O2 supplementation[14]. Intra-venticular hemorrhage (IVH) was diagnosed by cranial ultrasound examination that performed in all infants at days 5-7 by an experienced pediatric radiologist. Retinopathy of prematurity was diagnosed by an expert ophthalmologist by indirect ophthalmoscopic eye examination that initiated from age 4-6 weeks after birth.

Liver function tests (AST, ALT, ALP, and total and direct bilirubin), complete blood count (CBC) and blood urea nitrogen, creatinine were tested weekly during anti-fungal prophylaxis. Liver failure 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 about the studies' objective and patient's groups.

Statistical analyses were performed using the statistical package for social sciences (SPSS) version 20.0. (IBM SPSS Statistics Base 20. Chicago, IL: SPSS Inc). Quantitative data were presented as mean ±standard deviation (SD) and qualitative data as frequency and percent. Independent t test were used for testing continuous normally distributed data. Categorical data were compared between groups using Chi- square or Fisher exact test. Two tailed tests were used and a p. value less than 0.05 was considered statistically significant.



Results

A total of 120 preterm neonates included in this study that 53 were girls and 67 boys. The mean gestation age of enrolled infants was 28.26±1.45 weeks. The demographic characteristics of studied patients are shown in table 1. The most common maternal complication was pre-eclapmsia. Intubation and mechanical ventilation was done in 18(15%)neonates that 10(8.5%) were in group A. Interventions and procedures in patients shown in table 2.

Table 1: Demographic characteristics of studied infants in both groups.

Variable	Group A (fluconazole) n=60	Group B (nystatin) n=60	P.value
Gestation age, wk	28.45±1.41	28.03±1.56	0.45
Birth weight, gr	1169±125	1145±114	0.29
Gender boys, n (%)	44 (78%)	29(48%)	0.25
Apgar score 1 min 5 min	7.07±0.75	7.14±0.65	0.45
Delivery mode, C/S, n (%)	54 (90%)	47(78%)	0,08
IUGR	15(25%)	17(28%)	0.39
Maternal DM, n (%)	3	5	
Pre-eclampsia, n (%)	28	32	
PROM, n(%)	4	3	0.56
Oligohydramnius, n (%)	3 (%)	1(%)	0.27
Antenatal corticosteroid, n (%) no One dose two doses	20 15 25	20 30 10	0.07
Maternal antibiotics, (n%)	35(58%)	37(61%)	0.55

C/S=cesarean section, IUGR=intrauterine growth restriction, DM=diabetes mellitus, PROM=prolonged rupture of membranes.

Table 2: Medical managements and interventions in studied infants.

	Group A (fluconazole) n=60	Group B (nystatin) n=60	P value
Surfactant therapy, n(%)	57(95)	55(91.6)	0.44
Mechanical ventilation, n(%)	10(16.6)	8(13.3)	0.65
PICC, n(%)	26 (43.3)	25(41.6)	0.48
UVC, n(%)	26 (43.3)	25(41.6)	0.48
Intralipid, n(%)	41(68.3)	40(66.6)	0.80
Urinary catheter, n(%)	14(23.3)	11(18.3)	0.33
Broad spectrum AB, n(%)	7(11.6)	17 (28.3)	0.04

PICC= peripherally inserted central catheter, UVC= umbilical vein catheter, AB= antibiotics.

Systemic fungal infection was detected as positive fungal urinary infection in 6 (5%) studied infants that 3 patients were in group A, p= 0.99. Mortality reported in 3(2.5%) cases that was one in fluconazole group but it was not candida attributable.

Table 3: primary and secondary outcomes in studied patients.

	Group A (fluconazole) n=60	Group B (nystatin) n=60	P value
SFI, n (%)	3(5%)	3(5%)	0.99
ROP,n (%)	1(1.6%)	4(6.6%)	0.04
IVH, n (%)	7(11.6%)	3(5%)	0.02
BPD	12(20%)	20(33%)	0.14
Mortality, n (%)	1(1.6%)	2(3.3%)	0.55

SFI=systemic fungal infection, ROP= retinopathy of prematurity, IVH= intra- ventricular hemorrahage, BPD= bronchopulmonary dysplasia, NEC=necrotising enterocolitis.

Bacterial sepsis detected in 7 (5.8%) patients that 4 infants were in group B, P= 0.45. Severe stages of retinopathy of prematurity (ROP) was treated in 4(6.6%) patients in group B and one neonates (1.6%) in group A, p=0.04. Intra-ventricular hemorrhage was detected in brain ultrasound examination in 3 (5%) neonates in group B and 7 (11.6%) neonates in group A, p=0.02. BPD was determined in 20(33.3%) neonates in group B and 12(20%) patients in group A, P=0.14. NEC was not determined in none of studied patients, table 3. Any case of liver failure diagnosed in studied patients.

Discussion

The rate of systemic fungal infections and mortality were not significantly different among preterm infants with fluconazole or nystatin prophylaxis in our study. The complications of prematurity including advanced stages of ROP and BPD were significantly more common in preterm infants with nystatin prophylaxis, whereas IVH was more common in fluconazole group in this study.

Similar to our study, nystatin was effective as fluconazole in prevention of SFI in some studies.[13,15-18] Aydemir et al., compared intravenous fluconazole and oral nystatin with placebo in very low birth weight infants.[13] They demonstrated that nystatin prophylaxis resulted in decreased the gastrointestinal tract, skin, and respiratory tract Candida colonization. Invasive Candida infections were significantly lower in both the fluconazole and nystatin groups compared with the placebo group (3.2%, 4.3% vs. 16.5%, p < .0001).Unlike their study, we didn't have placebo group.

Rundjan and coworkers compared the fungal colonization and SFI among 95 preterm infants received oral nystatin and placebo. The incidence of fungal colonization was lower among infants innystatin group compared to those in control group (29.8 and 56.3%, respectively). There were five cases of SFI in the control group.[18] They concluded that the use of nystatin showed a potential protective effect against SFI among VLBW preterm infants without significant difference.

In our study 3 (5%) cases developed SFI that is less than 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 diference may be explained by lower gestation age of studied infants[19].

No significant adverse effects have been reported in infants treated with fluconazole prophylaxis such as bacterial infections, necrotizing entercolitis, focal bowel perforation, and cholestasis.[20-23]

Because of very high osmolality of oral suspension of nystatin (3002 mOsm/L), there is a concern with the use of this hyperosmolar medication and NEC. Aydemir et al, similar to our study, demonstrated no difference regarding NEC (8.6%, 9.6%, 9.9%) or mortality (8.6%, 8.5%, 12.1%)in fluconazole, nystatin and placebo groups, respectively.[13]

Some evidence favors fluconazole for antifungal prophylaxis owing to its greater efficacy compared with nystatin prophylaxis (80%-90% compared with 50-60%), its safety in VLBW infants, twice-weekly administration, intravenous administration in the case of gastrointestinal disease or hemodynamic instability and probably lower cost. Cost of the medications may vary by country and NICU. One dose of nystatin is less expensive than fluconazole. With comparing 3-4 doses per day of nystatin with twice a week of fluconazole, nystatin is more expensive for a complete course of prophylaxis .

However, the potential harms of routine antifungal prophylaxis include Candida resistance patterns, drug side effects and cost. There are studies that recommended fluconazole prophylaxis be limited to units with moderate-to-high incidence of invasive candidiasis since incidence of candidiasis is decreased in some NICUs.[21,24] The rate of SFI was low in our studied patients (5%) although we have not a placebo group. Zhang and co-workers 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, PVL/IVH in prophylaxis group.[25] In our study, the rate of BPD and severe ROP were significantly lower in group A with fluconazole prophylaxis than nystatin group. The results of Wang study suggested that the prophylactic use of fluconazole had no significant effect on the occurrence of common complications in preterm infants.[26] Significantly decreased colonization of Candida spp. in endotracheal secretion, nasopharynx, peri-umbilical region, perineum, gastric aspirate and skin reported in a meta-analysis of 7 previous studies.[27]

The limitations of this study were small sample size, lack of long term follow up of studied patients. Since prophylaxis started in first 24 hours of life the fungal colonization were not detected in included preterm infants in our study.

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.

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