Oral Nystatin Versus Intravenous Fluconazole as Neonatal Antifungal Prophylaxis: Non-inferiority Trial

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ABSTRACT

Background: Fluconazole has shown to be effective in reducing both colonization and invasive Candida infection (ICI) in ELBW neonates; we conducted a randomized trial to compare oral nystatin with intravenous fluconazole for prophylaxis against invasive Candidiasis in high risk neonates. **Materials and Methods:** By using SPSS, preterm less than 30 weeks gestation and/or birth weight 1200 grams or less assigned to receive either intravenous Fluconazole (6 mg/kg q72 hr for 1st week then q48 h for 6 wks) or oral Nystatin (100,000 unit q8 hr for 6 wks). The medications commenced at one week of age after obtaining the base line investigations and check for Candida colonization by urine culture and rectal swab; subsequently all lab work and the clinical data were monitered regularly. Risk factors were assessed. The data collected prospectively looking for primary end point the invasive Candida infection (ICI) and 2 ndry outcomes include medication safety, tolerance and cost. **Results:** 65 neonate randomly assigned however only 57 neonates comleted the study 33/57 (57%) to intravenous fluconazole group and 24/57 (42%) to oral nystatin group. No differences in birth weights Nystatin (1.15 Kg) Fluconazole (1.01 Kg), gender males (26/57), female (32/57), Gestational age (29.28 vs l28.22) or risk factors between the two groups. Rectal swab Colonization occurred in 2/24 (8%) in Nystatin group and 4/33 (12%) in the Fluconazole group, but none of the neonates developed ICI or side effects, although in the Fluconazole group transient transaminase elevation 2SD standard deviation above the mean was observed. Central line duration was 2 SD above the mean for fluconazole group, The cost of the Fluconazole treated group (7,581 SAR) 106.4 US/pt double the cost of Nystatin treated group (3,375 SAR) 50 US/pt. **Conclusion:** Intravenous Fluconazole and oral Nystatin at the prophylactic doses are equally effective and safe in preventing (ICI) in preterm neonates, however oral Nystatin is readily available, easily administered with lower cost per neonate.

Key words:
Candida, fluconazole, neonatal, nystatin, prophylaxis

INTRODUCTION

Invasive candida infection (ICI) is a significant health problem during the neonatal period. It is associated with high mortality and morbidity. Candida species is the 3rd most frequent causal agent of late onset sepsis in pre-term neonates,[1] with an estimated incidence of 1.6-9% in very low birth weight (VLBW) and of 10-16% in extremely low birth weight neonates (ELBW) in the Neonatal Intensive Care unit (NICU)[2-4] with crude mortality of 30-75%.[5]

Neonatal ICU at our center is a level 3; tertiary care facilities look after extremely preterm infants who are at high-risk for ICI. The incidence rate in our center is 9.7%.

Up until 2006 when we started using intravenous fluconazole prophylaxis for our VLBW and ELBW infants, it was our observation that the incidence of ICI had dropped significantly, which is in agreement with other results.[6,7]

Previous studies showed that anti-fungal prophylaxis reduces the risk of Candida infection in neonates.[7] Fluconazole is the most widely used anti-fungal agent for prophylaxis against ICI. Nystatin is another anti-fungal agent that has been used for prophylaxis of ICI in neonate;[8,9] it is readily available, easy to administer.

We undertook this study to test the hypothesis that oral nystatin is as effective and non-inferior to the intravenous fluconazole against ICI in VLBW and ELBW.

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tertiary care facility with level 3 NICU collaborated with our center to conduct this study, follow the same study protocol and data collection sheets. The study has been approved by both hospital institutional review board committees.

MATERIALS AND METHODS

A total number of 65 extremely pre-term neonates admitted to our centers were enrolled in the study between February 2011 and February 2012, with gestational age of 30 weeks or less, birth weight of 1200 g or less. By using the SPSS statistical software program random numbers were generated, and neonates were assigned to either arm A or arm B. Neonates in arm A received nystatin suspension at the recommended prophylactic oral dose, that is 1 ml (100,000 IU) every 8 h orally for 6 weeks[8,10] and neonates in arm B received intravenous fluconazole at the recommended prophylactic dose, that is 6 mg/kg every 72 h at the end of 1st week, then every 48 h from 2nd week to 6th week of life.[7]

The drugs administration commenced at the end of 1 week of age after obtaining the base line investigations, which include complete blood count (CBC), Transaminases (ALT, AST) serum creatinine, blood urea nitrogen, blood culture, urine culture and rectal swabs, subsequently have been carried out weekly until the study was over.

Risk factors for Candida colonization and infection were monitored carefully (broad spectrum antibiotics duration use, duration of Total Parental Nutrition (TPN), date of commencing oral feeding, H2 blockers, central line, corticosteroids and aminophylline).

The data were collected prospectively looking for the primary end point. The primary outcome was the incidence of ICI in infants receiving either fluconazole or nystatin, and the secondary outcome was the safety and costs of drug administration.

Neonates who developed a fungal infection proven by blood or urine cultures would be taken off the study and treated with appropriate antifungal medication such as amphotericin B or/and fluconazole at the standard therapeutic dose as recommended.

Data collecting sheets for every patient as per (data collection performa) were used.

Written parental or legal guardian consent was obtained for every patient before enrolment in the study.

Inclusion criteria

All preterm neonates 30 weeks gestation or less, weight 1200 g or less, born in our centers or transferred from other facilities.

Exclusion criteria

Neonates with severe congenital anomalies, fatal chromosomal anomalies, severe sepsis, disseminated intravascular coagulation, intraventricular hemorrhage, and persistent pulmonary hypertension of newborn, parents' refusal for their baby to be enrolled in the study or any other condition to the discretion of the investigators that the neonate may not be able to complete the study.

Sample size and statistical methods

The null hypothesis to be tested is that the effectiveness and safety of oral nystatin prophylaxis is not equivalent and inferior to the use of intravenous fluconazole prophylaxis in preventing ICIs in high risk VLBW and ELBW versus the effectiveness is not inferior. When the sample size in each group is 25, a two-group large-sample normal approximation test of proportions with a one-sided 0.050 significance level will have 80% power to reject the null hypothesis that oral nystatin and intravenous fluconazole are not equivalent (the difference in proportions, pT − pS, is −0.150 or farther from zero in the same direction) in favor of the alternative hypothesis that the proportions in the two groups are equivalent, assuming that the expected difference in proportions is and the proportion in the standard group.

Use of χ^2 test on contingency tables, the standard t test for independent samples and paired comparisons test for repeated measurements for evaluation of non-parametric data the Mann-Whitney U test will be used. Mantel-Haenszel test and logistic regression will be used to adjust for confounding variables.

RESULTS

A total of 65 infants were enrolled in the study. 3/65 (4%) infants could not complete the study, 2 developed severe bacterial sepsis and Disseminated intravascular coagulopathy (DIC), one had chromosomal anomalies (Edward Syndrome), 5/65 (7%) infants their parents refuse to sign the consent, so they were given the standard prophylaxis therapy in the NICU and excluded from the study [Figure 1].

57 infants completed the study, 24/57 (42%) in the nystatin group and 33/57 (57.8%) in the fluconazole group [Figure 2].

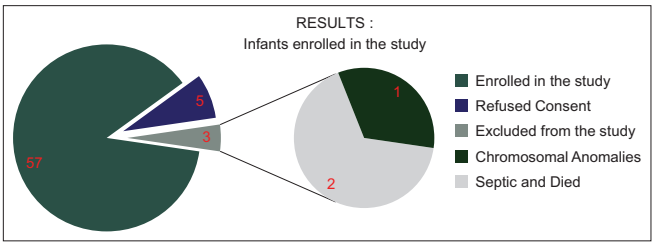

Figure 1: Infants enrolled in the study

The infants were matched for their gender (26 males and 31 females), gestational age mean (28.2 and 29.3) weeks, birth weight mean (1.0 and 1.1) kg, and discharged weight mean (1.7 vs. 1.8) kg; Both groups also matched for the duration of broad spectrum antibiotics (11.49 and 14.04) days, use of TPN (14.27 and 17.29), mean duration of H2 blocker (14.67 and 13.80) days and ventilator support [Table 1].

The safety profile and the adverse side-effects for both medications revealed renal profile, CBCD were normal all through the study. The transaminase (ALT) mean 10.86 and 37 I.U/ml for the nystatin and fluconazole respectively after the therapy commence and remained elevated all through the peek; however was week 3, it is 3 folds elevated in fluconazole group although both within normal ranges per our laboratory references [Figure 3].

2/24 (8%) infants in fluconazole group colonized with Candida albicans in initial rectal swabs and 4/33 (12%) in nystatin group; however, initial blood, urine cultures showed no growth and subsequently no Candida isolated [Figure 4].

No infant had ICI in either group.

However, 2/33 (6%) in fluconazole group died because of bacterial sepsis (Ascentobacter sepsis) excluded from the study, and 2/24 (8%) in the nystatin group developed *Escherichia coli* urinary tract infection requiring antibiotic treatment and continued in the study [Figure 5].

Central line duration however was 2SD above the mean in fluconazole group.

The cost of the fluconazole treated group was (2660 U$) 106.4 U$/infant, which is double the cost of nystatin treated group (1600U$) 50 U$/infant [Figure 6].

Table 1: Patients characteristics and risk factors

	Nystatin group *N*=24 (mean±SD)	Fluconazole group *N*=33 (mean±SD)
Sex		
Total	24	33
Males	11	15
Females	13	18
Gestational age (weeks)	(29.3±1.6)	(28.2±2.8)
Birth weight (kg)	(1.16±0.14)	(1.02±0.2)
Discharge weight (kg)	(1.8±0.3)	(1.8±0.27)
Duration of antibiotics (days)	(11.5±11)	(14.1±12)
TPN duration (days)	(14.3±10)	(17.3±9.9)
H2 blocker duration (days)	(15±23.6)	(13.8±10.8)
Central line duration (days)	(5±4.7)	(10.2±9.3)*
Ventilator support duration (days)	(8.3±12)	(12.8±10.6)
Transaminase (ALT)	(11±1.9)	(37±75)*

*Statistically significant; ALT – Transaminases; TPN – Total parental nutrition

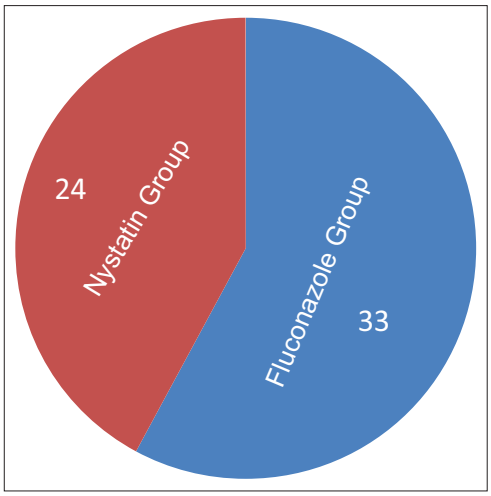

Figure 2: Nystatin and fluconazole groups

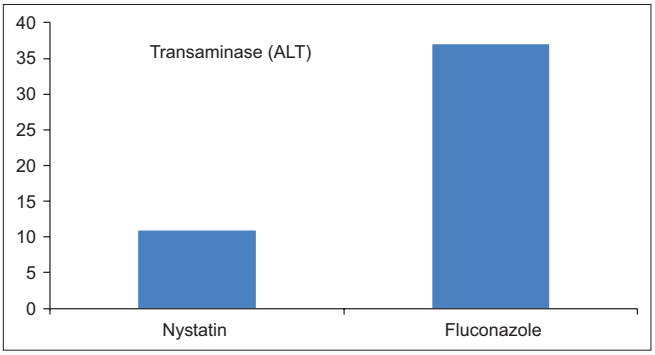

Figure 3: Transaminases

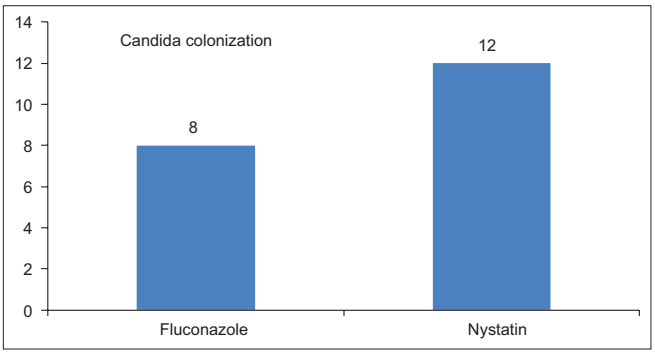

Figure 4: Candida colonization

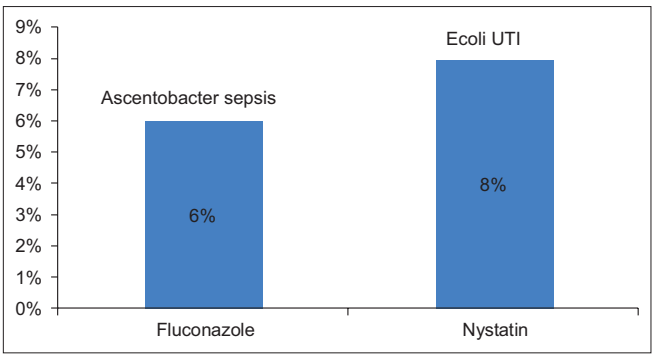

Figure 5: Sepsis in both groups

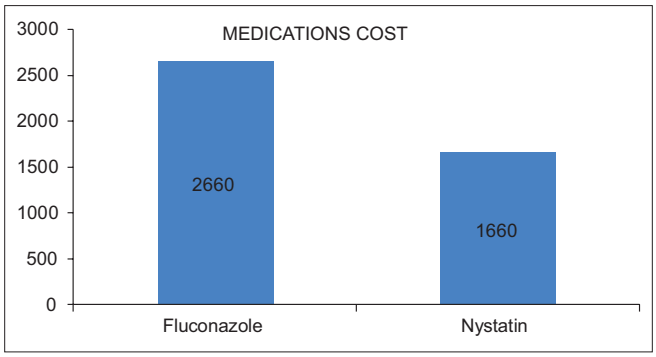

Figure 6: Medication cost

DISCUSSION

Although, there are controversial views about the general use of antifungal prophylaxis medication for ELBW in NICU, the potential of decreasing the incidence of ICI particularly in a unit with high incidence of candida infection makes use of a prophylactic agent to decrease the risk of colonization is attractive.[11] Small trials by Sims *et al*.[7] and Wainer *et al*.[10] of oral nystatin prophylaxis and oral myconazole gel prophylaxis both reported no difference in the incidence of ICI.

Chapman *et al*.[11] enrolled ELBW infants within the first 5 days of life in a study with the primary end point ICI, infants randomized to intravenous fluconazole group had no ICI versus 20% ICI for the placebo group.

Both fluconazole and nystatin have been shown to be effective as prophylactic against ICI in ELBW, and VLBW.[6]

In recent study Aydermir *et al*.[12] showed no statistically significant difference in the reduction of either invasive fungal infection or overall mortality between the fluconazole or nystatin groups.

The fluconazole use was associated with long duration use of central line, which may pre-dispose to systemic bacterial infection. We observed in our infants that 2/34 (5%) patients who develop severe sepsis were in the fluconazole group, but the development of sepsis could be related to multifactor. We notice; however, it did not affect the length of hospital stay.

Although hepatic transaminase was 3 folds higher in fluconazole group in comparison to nystatin group. This is similar to what have been reported in other studies[11,12] with no clinical complications. The level in both groups remained within the normal laboratory reference range.

2/25 (8%) in the nystatin group developed urinary tract infection with *E. coli*, we don't have explanations for this but the possibility is that sterilization of the gut with nystatin might have led to the overgrowth of the bacterial gut flora.

Our colonization rate was low which contributed to the lower incidence of ICI in our center and the MCH, only 6 infants colonized with Candida albicans (8% and 12.5%) in the fluconazole and nystatin groups respectively, this possibly related to the fact that most of our VLBW and ELBW were delivered by cesarean section.

None of the infants developed ICI. Our very restrict use of broad spectrum antibiotics in our unit, early start of enteral feeding, short use of TPN, might have contributed to lower incidence of Candida colonization and infections.

There are however few limitations to our study, our Candida infection incidence rate is low, and we have a very low colonization rate the gestational age in our sample are relatively higher mean 27 weeks. We recommend further randomized control multi-center trial with lower gestational age.

CONCLUSIONS

Both intravenous fluconazole and oral nystatin at the recommended doses are equally effective in preventing systemic Candida infection in preterm neonates in our study, no serious side-effects were observed to either of the medication; however, oral nystatin is readily available and easily administered with half the cost of fluconazole.

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