Research Article

Efficacy of Prophylactic Fluconazole Therapy in Preterm and Very Low Birth Weight Neonates in Preventing Invasive Fungal Infection

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Abstract

Background: Preterm and low birth weight infants have an immature immune system that predisposes them to infections. Broad-spectrum antibiotics, steroids, central venous catheters, endotracheal intubation, and abdominal surgery increase the risk of invasive candidiasis. Prophylactic fluconazole therapy may be helpful in the prevention of invasive candida infection.

Objective: To determine the efficacy of prophylactic fluconazole therapy in preterm and very low birth weight infants in the prevention of invasive candida infection.

Methods: A randomized clinical trial (ClinicalTrials.gov ID NCT05848492) was conducted at the Neonatal Unit of Services Hospital Lahore, Pakistan, from May 1st, 2021 to October 31st, 2021. A total of 110 neonates were recruited for the study. Neonates were divided into a fluconazole prophylaxis group and a control group. The efficacy of fluconazole was determined based on its ability to prevent the development of invasive candida infection. Data were collected using an online form created in Google Forms, and analysis was conducted using PSPP version 1.4 for descriptive data and Open Source Epidemiologic Statistics for Public Health (OpenEpi) version 3.0 for calculating p-values.

Results: The majority of the neonates were between 32 to 34 weeks of gestational age. Cesarean section was the most common mode of delivery (58.6%). 50% of the babies had a history of preterm premature rupture of membranes (PPROM). All infants received broad-spectrum antibiotics. 1 neonate in the fluconazole prophylaxis group while 3 neonates in the placebo group developed invasive candidiasis. Statistical analysis using the Yates-corrected chi-square test found no significant difference in preventing invasive candidiasis between the fluconazole group and the control group in the study population.

Conclusion: The study conducted at our center found that prophylactic fluconazole therapy did not show a significant difference in preventing invasive candidiasis in preterm and very low birth weight (VLBW) neonates.

Received: 24-10-2023 | **1st Revision:** 14-04-2024 | **2nd Revision:** 06-06-2024 | **Accepted:** 28-09-2024

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Keywords | Antifungal, fluconazole prophylaxis, fungal prophylaxis, invasive fungal infection.

Production and Hosting by KEMU

https://doi.org/10.21649/akemu.v30i4.5541

Introduction

Infection with candida can present as oral thrush, candida diaper dermatitis, or invasive candidiasis presenting as a sepsis-like illness.[1] Invasive fungal infec-

tion is the detection of candida species in blood, cerebrospinal fluid, or urine.[2] Clinical signs of invasive candidiasis may include lethargy, temperature instability, feeding intolerance, apnea, hypotension, respiratory distress, abdominal distension, and thrombocytopenia.[3] Fungal infection has been associated with an increased risk of retinopathy of prematurity and chronic lung disease.[4] Preterm and low birth weight infants have an immature immune system that predisposes them to infections with bacteria, viruses, and fungi.[5] These infants usually require prolonged admission in the neonatal unit and there is often a need for the administration of broad-spectrum antibiotics which predisposes them to colonization with fungi that may invade to cause systemic disease. Other risk factors for the development of invasive fungal infection include endotracheal intubation, abdominal surgery[6], the presence of a central venous catheter, administration of H2 antagonists, and steroids[7]. Infection with Candida species is the third most common cause of bloodstream infection in premature infants.[3] Mortality in preterm infants due to invasive candidiasis is around 20% and can be as high as 50% in infants weighing <1500g at birth.[3] Invasive candidiasis is the second most common infectious cause of death in extremely preterm infants. Prophylactic fluconazole given twice a week for 6 weeks has been shown to reduce colonization and invasive infection.[8] In a study conducted by EA Khan, et al it was found that out of 1550 neonatal admissions over 5 years in a tertiary care hospital in Pakistan, 49 (8.8%) neonates had positive blood cultures for Candida species out of which only 6 (21%) had received antifungal prophylaxis, and 10 (20%) cases died due to Candida sepsis including the death of 2 (4%) neonates who had received prophylaxis.[9] Afzal et al. found that out of 350 neonates having sepsis, 36 (10.2%) neonates had positive blood cultures for Candida species.[10] Mohd Yunus et al found that out of 526 neonates admitted with sepsis in the neonatal intensive care unit in India, 83 (15.7%) had invasive candidiasis with positive blood cultures.[11] Data from multiple neonatal intensive care units shows that the incidence of invasive candidiasis may vary significantly among similar units and uniform practice guidelines for prophylactic antifungal therapy cannot be designed.[12] Every neonatal unit may formulate institutional guidelines for fungal prophylaxis based on local data relating to invasive candida infections. This will prevent undue use of antifungal therapy reducing the financial burden on healthcare systems as well as prevent antifungal drug resistance. Moreover, it has been suggested by the Infectious Disease Society of America that fungal prophylaxis may be considered in extremely low birth weight neonates at centers with a high incidence of invasive candidiasis.[13] The present study was, therefore, conducted to determine the incidence of invasive candidiasis among preterm and very low birth weight infants in our neonatal unit and to evaluate the efficacy of prophylactic fluconazole in the prevention of invasive fungal infection. Based on the results of the present study institutional guidelines were designed in our neonatal unit relating to antifungal prophylaxis in preterm and very low birth weight infants.

Methods

After obtaining ethical approval from the Institutional Review Board (IRB), a randomized clinical trial (Clinical Trials.gov ID NCT05848492) was conducted in the Neonatal Unit, Department of Paediatrics at Services Hospital, Lahore, Pakistan from 1st May 2021 to 31st October 2021. A sample size of 90 was estimated using two proportion sample size calculations taking 90% power of study with a 5 % level of significance considering 17% cases of invasive candidiasis in the placebo group while 0% invasive candidiasis in the fluconazole prophylaxis group. The sample size was extended to 110 since it was anticipated that patients who may require completion of fluconazole prophylaxis at home after discharge from the hospital may be lost to follow-up.

Preterm babies born ≤ 34 weeks of gestation (based on the last menstrual period and Ballard scoring) and/or very low birth weight babies (weighing < 1500 g at birth) presenting to our unit within the first 72 hours of life were included in the study. Syndromic babies, babies with suspected or confirmed metabolic disorders, babies with raised liver enzymes, and babies presenting to our unit beyond 72 hours of life were excluded from the study.

Invasive fungal infection was defined as positive culture for candida species from normally sterile sites (such as blood or cerebrospinal fluid or urine) along with clinical features of candida infection i-e lethargy, poor feeding, apnea (cessation of breathing for more than 15 seconds) or tachypnea (respiratory rate of 60 or more),

bradycardia or tachycardia (heart rate <100 or more than 180, respectively), hypothermia (axillary temperature <96.5 °F), oral thrush, candida diaper dermatitis, seizures or abdominal distension with feeding intolerance.

Patients were divided into prophylactic and control groups, 55 patients in each group, using nonprobability sampling. In the prophylaxis group, an initial 12 mg/kg loading dose of fluconazole was given intravenously followed by 6 mg/Kg every 72 hours for a total duration of 6 weeks (42 days). When invasive fungal infection was diagnosed, the frequency was changed to 6mg/Kg/day in neonates ≤29 weeks gestation older than 14 days and in neonates ≥30 weeks gestation older than 7 days. For neonates with invasive fungal infection having gestational age ≤29 weeks up to 14 days of life and neonates ≥30 weeks gestational age up to 7 days of life the frequency was 6mg/kg every 48 hours. No treatment was advised to the control group.

Once the baby began to tolerate maximum enteral feeds, fluconazole was administered via the oral route. Blood and urine cultures (samples taken by clean catheterization), and CSF cultures in patients with suspected meningitis were sent to both the placebo group and prophylactic group before starting the treatment. Blood and urine cultures were repeated on day 14 and day 42 (optional) when holding prophylactic treatment. If there was a growth of candida in any culture along with signs of invasive candidiasis as discussed above, fluconazole at the therapeutic dose of 12 mg/kg/day was started. It was planned that in case growth of candida species resistant to fluconazole were to be obtained, treatment with amphotericin would be started. Fluconazole was considered efficacious if it prevented the development of invasive candida infection. Complete blood count (CBC), alanine aminotransferase (ALT, normal 40 IU/L), aspartate aminotransferase (AST, normal 35 to 140 IU/L), serum urea (normal up to 20 mg/dL), and serum creatinine levels (normal up to 1.2 mg/dL) were acquired on day 0, 14 and 42 of the treatment in prophylactic group. Prophylactic fluconazole therapy was stopped if serum ALT, AST, and urea were raised twice the upper limit and if serum creatinine was raised above 1.2 mg/dL.

Data were entered in an online form developed in Google Forms and laboratory results received over time were updated in the Google Sheets file linked with the form. Descriptive data such as the age of the neonate at admission, gender, gestational age, mode of delivery, place of delivery, antenatal steroids given to the mother, and antenatal antibiotics given to the mother were analyzed in PSPP version 1.4 from Free Software Foundation while the p-value was calculated using OpenEpi version 3.0.

Results

The study included a total of 110 participants, with 55 neonates assigned to the prophylactic fluconazole group and 55 neonates assigned to the control group. Table 1 elaborates on the characteristics of the patients.

When considering antenatal antibiotics, it was observed that 92 mothers (83.6%), while 18 mothers (16.4%) did not receive them. The history of preterm premature rupture of membranes (PPROM) was evenly distributed among the neonates, with 55 babies (50%) having a history of PPROM, and the remaining 55 babies (50%) not having such a history.

All 110 babies (100%) included in the study received broad-spectrum antibiotics as part of their treatment.

Blood culture results on admission showed that 97 babies (88.2%) had no growth in their cultures, 1 baby (0.9%) had Acinetobacter species, 3 babies (2.7%) had Klebsiella, 8 babies (7.3%) had Pseudomonas, and 1 baby (0.9%) had Serratia.

On day 14 of treatment, the majority of babies, 99 (90%), showed no growth in their blood cultures. However, 4 babies (3.6%) had Candida species, 1 baby (0.9%) had Acinetobacter species, 1 baby (0.9%) had Escherichia coli, 4 babies (4.5%) had Pseudomonas, and 1 baby (0.9%) had both Pseudomonas and Staphylococcus aureus.

Blood culture results on day 42 of treatment revealed that 81 (73.6 %) of the babies showed no growth, while blood culture could not be sent in 29 (26.4%) of the babies due to death before 42 days of life.

Among the study participants, 4 babies (3.6%) were diagnosed with invasive candidiasis, while the majority, 106 babies (96.4%), did not develop this condition. When looking at the outcomes of these 4 babies with invasive candidiasis, 1 baby died in the fluconazole group,

while in the placebo group, 1 baby with invasive candidiasis died and 2 babies with invasive candidiasis were discharged.

The overall outcome of the study participants showed that 29 babies (26.4%) died, and 81 babies (73.6%) were discharged. 3.6% of the preterm babies developed invasive candida infection. Deranged liver enzymes were not observed in any baby.

Table 1: *Patient Characteristics*

	Frequency	Percentage
Gender (n=110)		
Female	57	51.8%
Male	53	48.2%
Age at Admission (hours)		
1	102	92.7%
10	1	0.9%
24	3	2.7%
48	1	0.9%
72	3	2.7%
Gestational Age at Admission		
26 to 28+6	12	10.9%
29 to 31+6	32	29.1%
32 to 34+6	66	60%
Mode of Delivery		
C-Section	64	58.2%
SVD	46	41.8%
Place of Delivery		
Services Hospital Lahore	103	93.6%
Private clinic	4	3.6%
Maternity Clinic (Govt. Setup)	3	2.%
Weight		
Extremely Low Birth Weight (ELBW)	6	5.5%
Very low birth weight (VLBW)	53	48.2%
Low birth weight (LBW)	51	46.4%
Endotracheal intubation		
Yes	23	20.9
No	87	79.1
Umbilical Venous Catheterization (UVC)		
Yes	5	4.5%
No	105	95.5%

Table 2: *Neonates with Invasive Candidiasis*

Fluconazole group	1
Control group	3

Table 3: *Outcomes of neonates with invasive candidiasis*

Fluconazole group (1)	Death (1)	
Control group (3)	Death Discharged (2)	(1)

Data were entered into Open Source Epidemiologic Statistics for Public Health (OpenEpi) version 3.01 and a 2x2 table was generated. Among the infants in the prophylactic fluconazole group, 1 baby developed invasive candidiasis. In comparison, 3 babies were diagnosed with invasive candida infection in the control group. We employed the Yates-corrected chi-square test to analyze the data, and our findings revealed a chi-square value of 0.259. Furthermore, the two-sided p-value associated with this analysis was determined to be 0.6105. These results suggest that there was no statistically significant difference observed between the prophylactic fluconazole group and the control group in terms of preventing invasive candidiasis in the studied population of infant.

Discussion

There are multiple dosing regimens for fluconazole prophylaxis in preterm babies. In our study, we administered a loading dose of 12 mg/Kg followed by a maintenance dose of 6 mg/Kg every 72 hours for 42 days. A maintenance dose of 3 mg/Kg given twice weekly for 42 days or 6 mg/Kg given twice weekly for 42 days have been found equally effective in literature. These alternative regimens are supported by studies demonstrating their efficacy in maintaining therapeutic drug levels while minimizing potential toxicity, Similarly, the duration of therapy for 4 weeks in very low birth weight neonates and 6 weeks in extremely low birth weight neonates who have a more prolonged risk period for invasive candidiasis, are found to be equally effective.[14] The risk factors of invasive candidiasis discussed in the literature are prematurity, low birth weight, administration of broad-spectrum antibiotics, indwelling central catheters, endotracheal intubation, H2 antagonists, and steroid administration. These factors contribute to the disruption of normal flora and immune function, creating an environment conducive to fungal infections.[7] We observed that the preterm and very low-birth-weight babies admitted to our neonatal intensive care unit (NICU) were exposed to similar risk factors. In our study, 3.8% of the babies below 1.5 Kg weight developed invasive candida infection. The results, however, were not statistically significant and therefore, fluconazole prophylaxis in preterm and very-low-birth-weight infants was not effective in the prevention of invasive candidiasis in our institution.

In a retrospective observational study conducted by Gaffari Tunc, Arife Toksoz, and Fatih Kilicbay, nosocomial infection with candida in preterm babies was reported to be 1.6 % and mortality due to candida infection was found to be 35%.[15] Similarly, mortality due to candida infection in neonates has been reported to be 16.6%.[16] We found similar results with 3.6 % of babies developing invasive candida infection with 50% mortality due to invasive candidiasis. It aligns with the reported range of candida infection and the persistent threat of invasive candidiasis in preterm infants. There are multiple studies which have shown that fluconazole prophylaxis is effective in the prevention of invasive candidiasis in preterm and very low birth weight infants such as Anaraki et al had concluded that fluconazole prophylaxis reduced mortality and incidence of invasive candidiasis in preterm babies.[17] This suggests that proactive measures can significantly improve outcomes for these infants. Similar results have been reported by Robati et al in a systematic review supporting the efficacy of fluconazole prophylaxis.[18] Although multiple studies have highlighted the importance of prophylactic fluconazole therapy to prevent invasive candidiasis, Farreras et.al had concluded that fluconazole is prescribed without evidence of invasive candidiasis commonly, and national antifungal stewardship program should be formulated.[19] This indicates that the decision to implement prophylactic measures should be tailored to the specific infection rates and risk profiles of individual NICUs. Therefore, while fluconazole prophylaxis can be highly beneficial in high-risk settings, its universal application may not be justified in all contexts.

With an increasing percentage of candida-positive blood cultures in any center, the neonatologist, based on his/her statistical intuition, may expect the benefit of prophylactic fluconazole therapy. This expectation is grounded in the assumption that higher rates of candida-positive cultures correlate with a greater risk of invasive candidiasis, thus justifying preventive measures. Moreover, in the light of the recommendations of the Infectious Diseases Society of America antifungal prophylaxis may be considered in extremely low birth weight neonates at centers with a high incidence of invasive candidiasis.[13] This statistical intuition may lead to inappropriate use of prophylactic fluconazole in such centers where tests of significance are not applied on the available data or the study population is too small. With the rising percentage of cases of invasive candidiasis, our statistical intuition supported the use of fluconazole prophylaxis in preterm and VLBW neonates in our center, however, this intuition was proved wrong by the insignificant benefit of fluconazole prophylaxis in this study population as discussed earlier. Since the rates of invasive candidiasis vary greatly among institutions, antifungal prophylaxis should be considered based on the infection rates of every unit.[20]

In a meta-analysis that included 9 studies, Xie J has shown that 64 out of total 739 patients in the experimental group (8.6%) developed deranged liver enzymes due to prophylactic fluconazole therapy.[8] However, we did not note deranged liver enzymes in our patients receiving prophylactic fluconazole therapy. The incidence of invasive candidiasis can vary significantly among different neonatal units, highlighting the need for individualized institutional guidelines. It is crucial to consider local data and infection rates to develop effective strategies for antifungal prophylaxis. By implementing such guidelines, unnecessary use of antifungal agents can be avoided, reducing the financial burden on healthcare systems and preventing the emergence of drug resistance.

It is important to note that the study had several limitations that may have influenced the results. A larger sample size could have provided more statistical power to detect significant differences if they existed. The study was conducted at one center only, a multicenter study could have shown different results or reinforced the findings of the present study. Although the sensitivity of candida to fluconazole was reported by our laboratory, the facility of species identification for candida was not available at our setup. The empirical treatment of candida has led to the worldwide emergence of this particular resistant species. Therefore, it is important to interpret these results cautiously, considering the aforementioned limitations. Further research, particularly randomized controlled trials with larger sample sizes is needed to provide more robust evidence on the efficacy of prophylactic antifungal therapy in this population or to generalize the results.

Conclusion

Prophylactic fluconazole therapy did not demonstrate a statistically significant difference in preventing inva-

sive candidiasis in preterm and VLBW neonates in our center. However, due to the limitations of the study, further research is warranted to confirm these findings and provide more comprehensive insights into the effectiveness of prophylactic antifungal therapy in this population.

Ethical Approval: The Institutional Review Board, Services Institute of Medical Sciences, Lahore Pakistan approved this study vide letter No. Ref No. IRB/ 2020/ 746/ SIMS.

Conflict of Interest: The authors declare no conflict of interest.

Funding Source: None

Authors' Contribution:

ARB: Acquisition of data, analysis & interpretation of data, drafting of article, final approval

MTO: Conception & design, analysis & interpretation of data, critical revision for important intellectual content, final approval

TKB: Acquisition of data, critical revision for important intellectual content, final approval

MAS: Analysis & interpretation of data, drafting of article

SJ: Analysis & interpretation of data, final approval

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