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Efficacy of Fluconazole Prophylaxis on Invasive Candidiasis Infection in Extremely Low Birth Weight Neonates

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ABSTRACT

Background: Invasive candidiasis infection is one of the main life-threatening problems for extremely low birth weight (ELBW) neonates who are in the neonatal intensive care unit (NICU). Candidiasis can cause mortality, short-term morbidity, and long-term neurodevelopmental outcome in infected infants who survive. Therefore, since several years ago fluconazole prophylaxis has begun for premature newborns who were admitted to NICUs in some parts of the world.

Methods: In this retrospective cohort, the population study was all the infants of less than 1,000 gram admitted to Valiasr Hospital during the years 2011-2016. The subjects were divided into two groups of control and intervention. The control group did not receive any fluconazole prophylaxis, while for the test group, intravenous fluconazole was administered. Finally, we compared the incidence of candidiasis between the two groups.

Results: Fluconazole was administered to 70 out of 167 neonates. Our findings showed that two infants of the prophylaxis group (2.9%) and two (1.2%) of the non-prophylaxis group were infected with Candida species. The difference between the two groups was not statistically significant (P=0.501). Among the risk factors, bacterial sepsis, the duration of central catheter installation, total parenteral nutrition, meropenem or vancomycin administration, and hospitalization costs were significantly related to the incidence of invasive candidiasis infection.

Conclusion: The incidence of candidiasis in our study was 2.39% and fluconazole prophylaxis has not been effective in reducing fungal infections. Consequently, further investigations in larger sample sizes with different study settings and a variety of methodologies are needed to evaluate the efficacy of fluconazole prophylaxis on invasive candidiasis infection in ELBW neonates.

Keywords: Extremely low birth weight, Fluconazole, Invasive candidiasis infection, Prophylaxis

Introduction

One of the main life-threatening problems in premature infants, especially extremely low birth weight (ELBW) neonates who are in the neonatal intensive care unit (NICU), is infection by a variety of microorganisms, such as fungal infections. Colonized and invasive fungal infections (IFI) are often caused by different Candida species, especially *C. albicans* and *C. parapsilosis*. Colonization refers to the presence of positive fungal cultures from skin and urine without clinical symptoms. Moreover, IFI could be mucocutaneous candidiasis, blood infection, urinary tract infection, meningitis, peritonitis, and more uncommon types, such as arthritis and osteomyelitis.

Candidiasis can cause mortality, short-term morbidity, and long-term neurodevelopmental outcome in infected infants who survive. Various perinatal reasons are related to the development of invasive candidiasis, including the birth weight of less than 1000 gr, neutropenia, necrotizing enterocolitis (NEC), gastroschisis, surgery, congenital heart disease, wide-spectrum

antibiotics, central venous catheter, delayed onset of nutrition, prolonged ventilation, total parenteral nutrition (TPN), postnatal steroids, H2 blockers intake, maternal diabetes, cervical cerclage, and preeclampsia (1-3).

Developing the immune system, deficiency of surfactants, and skin permeability in the first two weeks after birth all contribute to the prevalence of Candida infection in premature infants (1). About 20% of fungal colonization may lead to an IFI (4). In terms of IFI, mortality is expected to be as high as 44% (5). In addition there are some probable complications, such as neurodevelopmental disorder, periventricular leukomalacia (PVL), premature retinopathy, and chronic pulmonary disease (1, 6).

Due to the mentioned consequences, fluconazole prophylaxis for premature infants has been begun in NICU centers around the world (7). Although some studies showed that the use of fluconazole did not play a role in reducing the IFI (2-3), in 2015 Ericson et al. found that fluconazole prophylaxis could diminish IFI (6). The prevention of infections in immature neonates has great importance and there is still no conclusive agreement on the utilization of fluconazole prophylaxis in NICU centers.

With this background in mind, we decided to investigate the relationship between fluconazole prophylaxis and candidiasis for a period of five years in Valiasr Hospital. The results of this study will lead to understanding the effects of fluconazole administration on preventing IFI in vulnerable infants, which can be useful in adopting a prophylactic protocol.

Methods

We performed this retrospective cohort study to evaluate the efficacy of routine fluconazole prophylaxis. The study population included all infants less than 1000 g who were admitted to Valiasr Hospital during 2011-2016. The subject and method of research were approved and confirmed by the Medical Ethics Committee of Tehran University of Medical Sciences with the code of IR.TUMS.IKHC.REC.13963042.

The data were collected through the neonatal registry system in Valiasr Hospital. The target population was divided into two groups of control and intervention. The control group received no fluconazole prophylaxis and the test group received 3 mg/kg intravenous fluconazole twice a week for six weeks. Fluconazole was applied to prevent IFI and was performed according to the guidelines of the hospital and was not implemented in courses.

The background variables included gestational age, birth weight, gender, the route of childbirth, and Apgar score. Risk factors considered to be chorioamnionitis, cervical cerclage, maternal diabetes or preeclampsia, steroid therapy during pregnancy, probiotics or H2 blockers prescription, bacterial sepsis, central venous catheter, ventilation, surgery history, TPN, late oral feeding, steroid therapy in the neonate, antibiotics therapy, and taking carbapenems, cephalosporins, and vancomycin.

The positive result of fungal culture from the skin, mucosa, blood, urine, cerebrospinal fluid (CSF), or tracheal discharge are the definitive diagnostic criterion for the outcome of fungal infection. The *SPSS* software version 18 was used to analyze the collected data and P-value < 0.05 was considered significant. In order to compare the variables, we used the Chi-square test.

Results

Out of the 3435 infants admitted during the 2011-2016 period in the NICU of *Valiasr* Hospital, 167 neonates had a birth weight of less than 1000 g. For 70 of these (42%), the prophylaxis of fluconazole was prescribed and the remaining 97 (58%) did not receive fluconazole. There was a significant difference between the two groups in terms of the history for H2 blocker intake, age of reaching full oral feeding, and mean days of receiving meropenem and vancomycin (Table 1).

Two infants (2.9%) in the prophylaxis group and two cases (2.1%) in the non-prophylaxis group were affected by IFI (P=0.501). Although the mean life span of dead neonates was 7.8±10 days, there was no significant statistical difference regarding the incidence of fungal infection among the 81 survived infants (P=0.365, Table 2).

Our findings showed that 38 infants (54.3%) from the prophylactic group and 41 infants (42.7%) in the non-prophylactic group had bacterial sepsis (P=0.25). All the four infants (100%) who had IFI and 36 infants (22.2%) from the non-infected group, had a history of bacterial sepsis (P=0.003). In other words, there was a significant correlation between bacterial sepsis and the development of IFI.

The mean number of the days of central venous catheterization was 9.2±13.75 days in the intervention group and 5.5±15.9 days in the control group (P=0.13). The infants with IFI with the mean of 26.25±10.21 days in the prophylactic group and 6.6±14.88 days in non-prophylactic group had catheter (P=0.01), As a result, it was

concluded that in the case of infection, the duration of the presence of venous catheter has been longer.

The TPN days had a mean of 19.01±20.49 and 15.01±19.51 days in the test and non-prophylactic groups, respectively (P=0.22). Moreover, the subjects with fungal infection had a mean of 36.25±18.39 days and the non-infected ones had

the mean of 16.23±19.80 days of receiving TPN (P=0.048). It was concluded that a longer duration of receiving TPN has a significant relationship with IFI occurrence. On the other hand, the neonates reached a full oral feeding in 42.87±22.50 days in the intervention group and in 29.72±20.26 days in the control group (P=0.01). Furthermore, the infants with infection in a mean

Table 1. Background variables and risk factors in the control and fluconazole groups (N=167)

Background variables and risk factors	Fluconazole group (N=70)	Control group (N=97)	P-value*
Gestational age (week)	1.9±27.7	27.79±2.1	0.84
Birth weight (g)	823±120.14	791±135.65	0.12
Gender			0.83
Female	30 (42.9%)	40 (41.2%)	
Male	40 (57.1%)	57 (58.8%)	
5-minute Apgar score	7.35±1.89	2.07±7.12	0.47
Normal vaginal delivery	8 (11.4%)	16 (16.7%)	0.34
Chorioamnionitis	3 (4.3%)	1 (1%)	0.17
Cerclage	4 (5.7%)	9 (9.3%)	0.39
Preeclampsia	21 (30%)	40 (41.2%)	0.13
Maternal diabetes	7 (10%)	6 (6.2%)	0.46
Maternal steroid therapy	45 (64.3%)	48 (49.5%)	0.057
Probiotics prescribing	5 (7.1%)	1 (1%)	0.08
H2 blockers prescribing	16 (24.2%)	7 (8.8%)	0.01
Bacterial sepsis	38 (54.3%)	41 (42.7%)	0.25
Mean duration of a central catheter (d)	13.75±9.2	15.95±5	0.13
Mean duration of a ventilator (d)	12.35±6.94	8.29±5.11	0.26
Mean duration of TPN (d)	20.49±19.01	19.51±15.01	0.22
Day of onset of oral feeding	11.17±10.19	9.9±7.25	0.23
Day of full oral feeding (≥100 cc/kg/day)	42.87±22.5	29.72±20.26	0.01
Mean duration of antibiotics therapy (d)	26±26.9	22.41±19.38	0.11
Mean duration of Meropenem prescribing (d)	9.41±15.23	4.17±10.01	0.02
Mean duration of Cephalosporin prescribing (d)	0	70.82±4.5	0.08
Mean duration of Vancomycin prescribing (d)	19.2±14.45	87.87±9.5	0.01
Fungal infection	2 (2.9%)	2 (2.1%)	0.501

*Chi-squared test

Table 2. Univariate analysis of clinical factors and invasive fungal infection (N=167)

Background variables and risk factors	IFI (N=4)	No IFI (N=163)	P-value*
Gestational age (week)	2.06±27.75	27.77±2.06	0.987
Birth weight (gr)	815±88.12	804±130.99	0.872
Gender			0.74
Female	2 (50%)	68 (41.7%)	
Male	2 (50%)	95 (58.3%)	
5-minute Apgar score	7	2.01±7.22	0.165
Normal vaginal delivery	1 (25%)	23 (14.2%)	0.54
Chorioamnionitis	0	4 (2.5%)	0.75
Cerclage	1 (25%)	12 (7.4)	0.31
Preeclampsia	2 (50%)	39 (36.2%)	0.571
Maternal diabetes	1 (25%)	13 (8%)	0.426
Maternal steroid therapy	4 (100%)	89 (54.6%)	0.07
Probiotics prescribing	0	6 (3.7%)	0.696
H2 blockers prescribing	1 (25%)	22 (155%)	0.6
Bacterial sepsis	4 (100%)	75 (46.3%)	0.003
Mean duration of a central catheter (d)	26.25±10.21	6.6±14.88	0.01
Mean duration of a ventilator (d)	9.4±13.5	10.13±5.6	0.12
Mean duration of TPN (d)	18.39±36.25	16.23±19.8	0.048
Day of onset of oral feeding	29±6.9	10.66±5.54	0.942
Day of full oral feeding (≥100 cc/kg/day)	39.66±21.21	22.28±35.27	0.739
Mean duration of antibiotics therapy (d)	45.75±18.66	21.64±24.5	0.057
Mean duration of Meropenem prescribing (d)	25.75±15.73	5.90±12.31	0.002
Mean duration of Cephalosporin prescribing (d)	3.75±7.5	3.32±0.39	0.057
Mean duration of Vancomycin prescribing (d)	27±23.36	14.56±10.35	0.029
Necrotizing Enterocolitis	1 (25%)	18 (11%)	0.38

*Chi-squared test

Table 3. Neonatal complications in both neonate groups based on the invasive fungal infection (N=167)

Neonatal complications	IFI (N=4)	No IFI (N=163)	P-value[*]
Brain ventricular hemorrhage	4 (100%)	63 (38.6%)	0.27
Cholestasis	0	7 (4.3%)	0.64
Mortality	2 (50%)	84 (51.5%)	0.95
Mean of admission cost (IRR)	35401441	10241857	0.013
Mean of admission duration (d)	47.25	30.51	0.27
Bronchopulmonary dysplasia	0	7 (10.4%)	0.833

*Chi-squared test

of 39.66±21.21 days and non-infected ones in 35.27±22.28 days reached this level of nutrition (P=0.739).

The mean duration of receiving meropenem was 9.41±15.23 days in the prophylaxis group and 4.17±10.01 days in the non-prophylactic group (P=0.02). Therefore, in those with IFI the mean of days receiving meropenem was 25.75±15.73 days and in the non-infected ones was found to be 5.9±12.31 days (P=0.002).

The mean duration of taking vancomycin was 14.45±19.2 and 7.87±9.58 days in the test and control groups, respectively (P=0.01). In addition, the IFI infants received vancomycin for 27±23.36 days and the non-infected ones received it for 14.56±10.35 days (P=0.029). Consequently, it was concluded that the longer duration of treatment with meropenem and vancomycin could be considered as risk factors for IFI.

The newborns with IFI and the non-infected ones were compared in terms of intraventricular hemorrhage (IVH), cholestasis, bronchopulmonary dysplasia (BPD), NEC, mortality, average costs, and hospitalization duration (Table 3). The average cost of admission for neonates with IFI was 33098831.9 IRR and for the non-infected group, it was 19271073.3 IRR (P=0.013), which showed a significant increase in admission fees in the cases of fungal infection.

Discussion

Our retrospective study was performed on 167 ELBW neonates admitted to NICU. A total of 70 newborns (41.92%) received fluconazole prophylaxis and four infants became infected with fungal infections two of which were in the prophylaxis group (2.9%) and two cases were in the non-prophylaxis group (2.1%). This can be concluded that the prevalence of fungal infection in our center was not high and fluconazole prophylaxis has not been effective in reducing fungal infections.

Therefore, the decision of prophylactic fluconazole prescribing should be based on determining the percentage of an outbreak. Although the mean survival time of the 86

(51.5%) dead neonates was 7.8±10 days, there was no significant statistical difference regarding the incidence of fungal infection among 81 survived infants (P>0.05).

In 2012, the European Society of Clinical Microbiology and Infectious Diseases suggested that fluconazole prophylaxis should be used in the case of fungal infections with the prevalence of above 2%. On the other hand, some articles suggest that prophylaxis should be carried out in prevalence of more than 15% (2-3, 5-6). With all the above interpretations, the prevalence of infection in our center was 2.39% and there was no significant difference between the two groups of exposure and non-exposure. As a result, routine fluconazole prophylaxis to infants under 1000 g in this center will not have justification.

One of the important risk factors for ELBW infants being infected with fungal infections is the presence of a central venous catheter. In the current study, the duration of having a central venous catheter had a significant relationship with the development of fungal infections. The mean number of days of existence of catheter in infants without infection was 6.6 days and in the infected ones was 26.2 days. In addition, all four infected newborns (100%) had central venous catheters.

Aliaga et al. in a prospective study, gathered the information of 709325 infants in 322 NICUs. These authors demonstrated that there was a significant relationship between the presence of central catheter and infection (8). In the study completed by Healy, the incidence of candidiasis infection in the period of fluconazole prophylaxis was evaluated compared to the other durations. The results revealed that the duration of using the catheter and the incidence of fungal infection were interrelated (5). In the study performed by *Lee* et al., there was no correlation between the presence of umbilical catheter on the third day after birth and the incidence of infection (3).

In another study in 2007, 99 newborns receiving preventive fluconazole were compared with 163 control cases. The duration of inserting a central catheter in the two groups was significantly different. However, the duration did

not have a significant relationship with IFI (6). The variation in the results of these studies explains the need for a large study concerning the relationship between catheterization and IFI in infants admitted to NICUs. In our study, bacterial sepsis had a direct relationship with the development of fungal infections, which was in line with the findings of Aziz et al. (9). Nonetheless, in other studies this relationship was not found to be significant (2-3, 6, 10).

Antibiotics therapy has been assessed in our study as well as in the previous investigations. In one study, there was a significant relationship with fungal infection (8). In the present study, the duration of treatment with meropenem and vancomycin had a significant relationship with fungal infection. However, some previous studies showed that there was not a significant correlation (3, 6, 10-11). There is a competition between Candida species and bacteria for growth, replication, and invasion of the body tissues. Therefore, the use of wide-spectrum antibiotics can lead to overcoming fungal infections. Culture test and antibiogram prevent unnecessary administration.

In our study, one of the cases that was related to being infected by IFI was the duration of receiving TPN. In the investigation carried out by Benjamin, there was a significant relationship between TPN days and fungal infection (2), while in two other articles no correlation was observed (4, 10). The age of full oral feeding (more than 100 cc/kg/day) was not associated with the presence of fungal infections in infants that were admitted to our department. On the other hand, the mean age of complete oral nutrition showed a significant difference between the two groups of exposure and non-exposure. In another study, it was indicated to be significant (3).

Undoubtedly, eliminating and shortening the duration of medical interventions and early oral feeding prevent the occurrence of complications, such as invasive infections in vulnerable infants admitted to the NICUs. This point should be taken into consideration for any newborn exclusively.

The incidence of fungal infections increases the cost of admission. However, the duration of admission did not significantly elevate. In three studies, this relationship was investigated showing no significant relationship between these two factors (2, 4). Preventive intervention with fluconazole regarding the prevalence of IFI in each center can be associated with lower costs for treatment and admission. Furthermore, prophylaxis and unnecessary antimicrobial

therapy should also be avoided.

Conclusion

Given the low prevalence of fungal infections in ELBW infants in our study and the different findings in other studies, it seems that the decision of using fluconazole prophylaxis in each center should be based on the percentage of fungal infections in that center. Moreover, in adults, the fungal culture is performed with a high volume of blood samples and the sensitivity will be 30%, while in infants it is completed with less volume of blood samples leading to lower sensitivity.

It should be noted that the use of broad-spectrum antibiotics, long catheterization, and the prolongation of TPN can be responsible for the occurrence of fungal infections. Therefore, caution should be exercised in prescribing them to reduce the cost of hospitalization resulting in assisting health economics. According to the results of this study, we recommend conducting this research with a different design in other centers or in multicenter mode to provide a more accurate picture of IFIs, effects of fluconazole prophylaxis, and evaluation of risk factors.

Acknowledgments

Conflicts of interests

The authors declare that there is no conflict of interest.

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