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Therapy report

ROUTINARY FLUCONAZOLE PROPHYLAXIS IN VLBW NEONATES: IS A RIGHT CHOISE?

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Summary

This is a retrospective cohort study with the aim of evaluating fluconazole efficacy in preventing invasive fungal infections in very low birth weight newborns, in our NICU setting.

Neonates weighing less than 1500g at birth, born between January 2013 and December 2014, were enrolled in the study.

The primary aim was to assess the prevalence of fungal infections. The secondary aim was to identify newborns with a higher risk of invasive fungal infections as well as the incidence of complications after invasive fungal infection.

59 newborns were included in the study. Routine fluconazole prophylaxis at the dose of 3mg/kg i.v. every 72 hours was administered to 47/59 (79,7%). The overall proportion of invasive fungal infections was 17%, with no significant difference between neonates who underwent fluconazole prophylaxis (19,1%) and those who did not (8,3%) (p = 0,4). *Candida parapsilosis* was the most common isolated strain (90%).

Lower gestational age, lower birth weight, surgery interventions and delayed initiation of enteral feeding were associated with invasive fungal infections.

All septic newborns developed complications: bronchopulmonary dysplasia, retinopathy of prematurity and periventricular leukomalacia. None died due to Candida infection.

Our findings do not appear to support routine fluconazole prophylaxis in very-low-birth -weight infants.

Introduction

Invasive fungal infections (IFI) are an important cause of mortality and short/long-term morbidity in very low birth weight infants (VLBW < 1500g) [6].

IFI incidence has been reported from 1% to 10%, according to various large cohort studies and all authors report an inverse relationship between both gestational age and birth weight and IFI. Differences between centers may be the result of different clinical practices and of the number of extremely low birth weight infants (ELBW < 1000g) admitted to each Neonatal Intensive Care Units (NICU) [2].

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In the last two decades, routine use of intravenous fluconazole in NICU, as a chemoprophylaxis, has been supported in the literature [4]. In 2013, seven trials involving 880 infants comparing fluconazole prophylaxis versus placebo or no drugs, were analysed by the *Cochrane Neonatal Group* [2].
Meta-analysis did not find any statistically significant difference in mortality, but did find a statistically significant reduction of IFI in VLBW infants who received intravenous fluconazole as a chemoprophylaxis (RR: 0,41; 95%CI: 0,27 - 0,61). Despite the 95 % confidence intervals, results have to be applied cautiously, since the incidence of IFI in the control group was higher (16%) than that reported in large cohort studies. Thus, this effect size may be overestimated in NICUs where the incidence of IFI is lower. A need for local surveillance, in order to detect the incidence of IFI, before initiating fungal prophylaxis, was suggested.

Material and methods

A retrospective cohort study of the clinical records of all VLBW newborns, admitted to the NICU of the Policlinico University of Bari, Italy, between January 2013 and December 2014, was performed, in order to evaluate fluconazole prophylaxis efficacy in this population.
The following data were examined: date of birth, gestational age, birth weight, sex, delivery mode, 1' and 5' Apgar scores, use and duration of fluconazole prophylaxis, antifungal therapy, use and duration of antibiotics, central venous catheter insertion and duration, fungal sepsis evidence, parenteral nutrition need and duration, mechanical ventilation need and duration. Other data, related to outcomes, including bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and retinopathy of prematurity (ROP), were also collected. IFI was defined by a positive culture of blood or cerebrospinal fluid.
Data from each patient were entered into a database using the File Maker Pro software and analyzed with the statistical software STATA MP11.
Continuous variables were presented as mean with indication of standard deviation (SD) and range; categorical variables as number and percentage.
Univariate statistical analysis was performed using Student's t-test for continuous variables and z-test for proportion for categorical variables. Relative risks were also calculated and 95% Confidence Intervals (95% CI) were indicated.
For all tests a p-value < 0,05 was considered statistically significant.

Results

Of the 84 neonates admitted to our NICU, 25 were excluded, for various reasons: outborn (12), unavailability of data (7) other major pathologies at birth (2) death within the first 3 days of life (4).
Fifty-nine infants were then included in the study as reported in table 1.
47/59 (79,7%) received routine fluconazole prophylaxis at a dosage of 3 mg/kg i.v. every 72 hours, for an average duration of the prophylaxis of 8,8 days.
Overall frequency of invasive fungal infections was 10/59 (17%), with no significant difference between neonates who underwent fluconazole prophylaxis (19,1%) and those that did not (8,3%) (z= -0,9; p = 0,4). *Candida parapsilosis* was the most common isolated strain (90%).
Newborns who developed IFI were usually treated with intravenous amphotericin B at the dosage of 5 mg/kg/die for an average duration of treatment of 17,4 days.
Four infants were then treated with micafungin, because the treatment with amphotericin B was ineffective, despite the *in vitro* sensibility of the isolated strain.
Gestational age (t=2.8; p<0,01), birth weight (t=3.6; p<0,01), surgery (RR:3.8; CI95%: 1.3-10.9; p<0,01) and duration of parenteral nutrition (and consequently presence and duration of venous catheters) (t=-2,8; p<0,01) were the most important risk factors for development of IFI.
BPD (100%; z=-4.2; p<0,01), IVH (70%; z=-3.6; p<0,01) and ROP (60%; z=-2.4; p=0,02) were significantly

greater in infants who developed IFI versus those who did not.
Mortality attributable to Candida was 0%.

Discussion

In 2013, Pandolfini *et al*. carried out an Italian survey on the use of fluconazole for prophylaxis of IFI in neonates, in order to describe the differences among national NICUs. Among Italian participant NICUs, 79% declared the use of fluconazole, with wide variations in its indications. Overall, no significant correlation was found between the use of fluconazole prophylaxis and the incidence of IFI [5].
Our data confirm the conclusions of this survey. We are aware that a 19,1% incidence of IFI, despite prophylaxis, is very high, but our retrospective study suggest that routine fluconazole prophylaxis may be ineffective in preventing invasive fungal infections, consistent with other research [3].
It is important to obtain further data regarding the efficacy of fluconazole prophylaxis in VLBW, in order to assess the possibility of the development of resistant fungal strains.
Fundamental practices such as the increased use of line bundles, better and earlier feeding practices and improved handwashing may contribute to the reduction of IFI in newborns, so that the routine use of fluconazole prophylaxis could be reserved only to neonates at major risk of IFI, i.e. ELBW and surgical VLBW neonates.
At the moment, the current lack of data on neonatal fungal infection prevention can be overcome only by well-designed randomized controlled trials and further studies in neonatal intensive care units are needed in order to validate any new antifungal strategies.

• No of patients	59
• Gender (male/female)	31/28
• Vaginal delivery, n (%)	6 (10%)
• Gestational age (mean, DS)	29,5 (±2,6)
• Gestational age, n (%)	
< 32 w	52 (88%)
>32 w	7 (12%)
• Birth weight, mean (DS), g	1150 (±249)
• Birth weight, n (%)	
1000 < BW <1500	44 (74,6%)
<1000	15 (25,4%)
• Central venous line positioned, n (%)	
• Intubation, n (%)	15 (25,5%)
• Major surgery , n (%)	6 (10%)
• Invasive fungal infection, n (%)	10 (16,9%)
• Invasive fungal infection onset, mean (DS), dol	2,9 (±5,5)
• Minimal enteral feeding, mean (DS), dol	47 (79,7%)
• Fluconazole prophilaxis, n (%)	8,8 (±5,9)
• Fluconazole prophilaxis, mean (DS), d	
ROP, n (%)	17 (28,8%)
BDP, n (%)	24 (40,7%)
IVH, n (%)	15 (25,7%)

Table 1. Neonate Characteristics

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