

Effects of Cessation of a Policy of Neonatal Fluconazole Prophylaxis on Fungal Resurgence

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Fluconazole has been used as prophylaxis against systemic fungal infections in preterm neonates. We conducted a study to determine whether cessation of a policy of prophylactic fluconazole results in a resurgence of fungal infections in a unit.

Neonates born in the 3 epoches: A 36-month pre-Fluconazole prophylaxis epoch (Group 1), a 21-month Fluconazole prophylaxis epoch (Group 2) and a 39-month post-Fluconazole prophylaxis epoch (Group 3) were compared for incidence and onset of fungal sepsis and resistance patterns.

There was a decline in the incidence of fungal sepsis from Group 1 to Group 2 ($P < 0.0001$), and it remained stable from Group 2 to Group 3 ($P = 0.99$). There was no significant difference in resistance to Fluconazole and to any of the azoles in Groups 1, 2 and 3 respectively. The mean age of onset of fungal sepsis got advanced from 10.21 ± 4 days in Group 1 to 16.60 ± 7 days in Group 2 [mean difference 6.4 days; 95% CI: 2.5, 10.3 $P = 0.002$] and returned back to 10.7 ± 5 days in Group 3 [mean difference -5.9 days; 95% CI: 0.2, -12.1 ($P = 0.06$)].

Key words : Fungal infection, Fluconazole prophylaxis, Resistance.

NEWBORN infants, especially Very Low Birth Weight (VLBW), are at risk for fungal infections(1-3). In our unit, prior to 1998, invasive fungal infections were common, with 1.32% of all live-births and 10% of all VLBW babies being affected. Studies in neonates suggest a role of prophylactic fluconazole in preventing fungal infections(4). What is still not known is whether or not the policy of prophylactic fluconazole should be continued uninterrupted in a neonatal intensive care unit (NICU). Although, previous studies have reported no increase in anti-fungal resistance during study periods ranging from 13 months to 30 months, there is no guarantee that

resistance will not increase if the policy of prophylactic Fluconazole is continued for longer periods(5,6). With this in mind we conducted a retrospective study to evaluate whether the reduction in incidence of fungal infections persists after the policy of prophylactic fluconazole is stopped.

Subjects and Methods

This retrospective study was conducted in the Level III neonatal unit of a tertiary care hospital in north India. From the database of a 96-month period (January 1995 to December 2002) we extracted case records of fungal sepsis proven by blood or supra-pubic urine culture. There were no cases of fungal

meningitis in this period. In the period from January 1998 to September 1999, as a unit policy prophylactic intravenous fluconazole (6 mg/kg/d) was given to those neonates who received intra-venous fluids, from birth till a maximum of day 5. From our earlier unit data, we had felt that fungal infections were occurring early on in life and mostly in those receiving IV fluids. This was the logic behind choosing 6 mg/kg/d from birth till day 5 to those on IV fluids. Thus, our regime was not similar to regimes that were reported later in 2001.

There were neonates born in 3 epochs: A 36-month pre-Fluconazole prophylaxis epoch (Group 1), a 21-month Fluconazole prophylaxis epoch (Group 2) and a 39-month post-Fluconazole prophylaxis epoch (Group 3). The 3 epochs were compared for incidence and time of onset of fungal sepsis, distribution of species and resistance patterns, based on the NCCLS guidelines(7). We analyzed risk factors of fungal infections: prematurity, low birth weight, admission to NICU, exposure to broad spectrum antibiotics and ventilation. The use of Total Parenteral Nutrition and post-natal steroids was too infrequent in our unit to merit analysis.

Categorical variables were compared between 2 groups by Chi square test with Yates correction or Fisher's Exact Test, as applicable. The trend of categorical variables across 3 groups was analyzed by Chi square test for linear trends. Normally distributed numerical variables were compared using Student's t test.

Results

There were 9224, 5477 and 9931 live births during the pre-prophylaxis, prophylaxis and post-prophylaxis epochs respectively. The prematurity rate, the VLBW rate, admission to the NICU, the usage of broad-spectrum antibiotics and ventilation increased from Group 1 through Group 3, as shown in *Table I*.

A total of 160 babies had fungal sepsis during the study. Of the 160 fungi isolated, species identification was done in only 93; of which 90 were *Candida* species and the rest were *Aspergillus* spp. There was a significant decline in the incidence of fungal sepsis from Group 1 to Group 2 ($P < 0.0001$), and it remained stable from Group 2 to Group 3 ($P = 0.99$). On sub-group analysis, the incidence among the VLBW babies also declined from

TABLE I—Comparison of Demographic and Risk Factors for Fungal Sepsis

Parameter	Pre-Fluconazole Group 1	Fluconazole Group 2	Post-Fluconazole Group 3	P value*
Live births	9224	5477	9931	-
Live births/year	3081	3130	3056	-
Males	5076 (55)	3054 (55.8)	6144 (61.2)	<0.0001
Admissions to NICU	2597 (28)	1939 (35)	3277 (33)	<0.0001
Premature	2767 (30)	1917 (35)	3575 (36)	<0.0001
VLBW	629 (6.8)	446 (8.1)	934 (9.4)	<0.0001
Antibiotics used	840 (9.1)	604 (11.2)	1241 (12.5)	<0.0001
Ventilation	358 (3.9)	348 (6.4)	477 (4.8)	0.004

Figures in parentheses are percentages. * = χ^2 for linear trends across 3 groups.

Group 1 to Group 2 ($P < 0.0001$), but remained stable from Group 2 to 3 ($P = 0.21$). Similar was the case with non-VLBW babies, the incidence declining from Group 1 to Group 2, but stable from Group 2 to 3.

There was no significant difference in resistance to Fluconazole and to any of the azoles in Groups 1, 2 and 3 respectively. While 11 cases of *Candida albicans* were reported in Group 1, no case was isolated after Fluconazole prophylaxis was started, *i.e.*, in Groups 2 and 3.

The mean age of onset of fungal sepsis got advanced from 10.21 ± 4 days in Group 1 to 16.60 ± 7 days in Group 2 [mean difference 6.4 days; 95% Confidence interval: 2.5, 10.3; ($P = 0.002$)] and returned back to 10.7 ± 5 days in Group 3 [mean difference -5.9 days; 95% Confidence interval: 0.2, -12.1 ; ($P = 0.06$)].

Discussion

In our study, the incidence of fungal sepsis declined significantly following the implementation of a policy of 5 days prophylactic Fluconazole and it did not show a resurgence

after stoppage of the policy. The decline and lack of resurgence was observed despite an increase in the prevalence of risk factors of fungal sepsis over time, *viz.*, prematurity, VLBW, admission to the NICU, usage of antibiotics and ventilation.

Two randomized controlled trials have evaluated the role of Fluconazole prophylaxis in neonates. Kaufman, *et al.*(5) reported that intravenous prophylactic Fluconazole completely eliminated invasive fungal infections and decreased fungal colonization by 38%, when administered to extremely low birth weight babies as long intra-venous access was available. Kicklighter, *et al.*(6) showed that prophylactic Fluconazole upto day 28 reduced Candidal colonization in VLBW infants, however, there was no effect on the incidence of invasive fungal infections. A meta-analysis of the above 2 studies demonstrated a significantly reduced risk of invasive fungal infection in the infants who received Fluconazole prophylaxis [typical relative risk: 0.20 (95% confidence interval 0.06, 0.67)]. Our study design differed from these 2 trials in that, ours was a retrospective

TABLE II—Comparison of Incidence and Characteristics of Fungal Sepsis Episodes

Parameter	Pre-fluconazole (Group 1) (n = 9224)	Fluconazole (Group 2) (n = 5477)	Post-fluconazole (Group 3) (n = 9931)	Group 1 vs 2 P value	Group 2 vs 3 P value
Fungal sepsis	122 (1.32)	14 (0.25)	24 (0.24)	<0.0001	0.99
Fungal sepsis in VLBWs	64 (10)	8 (1.8)	8 (0.85)	<0.0001	0.21
Fungal sepsis in non-VLBW	58 (0.67)	6 (0.12)	16 (0.18)	<0.0001	0.53
Mean age of onset* (days)	10.2 ± 4	16.6 ± 7	10.7 ± 5	0.002	0.06
Species identified*	72/122 (59)	7/14 (50)	14/24 (58)	0.71	0.87
Azoles resistance [#]	27/72 (37.5)	2/7 (29)	5/14 (35)	0.99	0.99
Fluconazole resistance [#]	12/72 (17)	1/7 (14)	2/14 (14)	0.99	0.99

Figures in parentheses are percentages; * = calculated among those who had fungal sepsis; # = calculated among those who had fungal species identification.

Key Messages

- A policy of administering prophylactic fluconazole to neonates on intravenous fluids decreased the incidence of fungal sepsis in the neonatal unit.
- There is no resurgence in the incidence of fungal sepsis once the policy of administering prophylactic fluconazole is stopped.

study, we administered Fluconazole to all those who received intra-venous fluids irrespective of gestational age and we used a 5-day course.

In our study there was no resurgence of fungal sepsis after the prophylactic Fluconazole policy was stopped. The fungal sepsis rate remained almost unchanged at 0.24% over the 39-month post-prophylaxis period. With an increase in the baseline post-natal risk for fungal sepsis one would have expected a rise in fungal sepsis in Group 3, which did not happen in our study.

The reason for lack of resurgence may be one of the following: either, (a) the prophylactic use of Fluconazole for 21 months may have interrupted transmission and reduced environmental fungal reservoirs within the unit, producing a residual effect, or (b) there was a secular trend towards a decline in fungal sepsis which was independent of fluconazole use. We also observed an advancement in the mean time of onset of fungal sepsis by 6.4 days from Group 1 to Group 2. This may suggest that the initial 5-day course reduces only early transmission, thereby delaying the mean time of onset. With the withdrawal of the policy, the mean age of onset expectedly returned to pre-prophylaxis levels.

A major consideration with anti-microbial prophylaxis is the potential for the emergence of stable resistance to the anti-microbial agent. Our study had limited data on which to

base any conclusions on change in trend of fluco-nazole resistance. However, investigators who used much higher cumulative doses than ours also did not find any significant changes in the minimal inhibitory concentrations of Fluconazole in fungal isolates during their study period(5,6).

Our study, being retrospective in nature with non-concurrent controls, had certain limitations. Data regarding the actual number of subjects who received prophylactic Fluconazole in each epoch and duration of prophylaxis in individual subjects were not retrievable. Thus we could comment about the overall incidence of fungal sepsis among neonates delivered in our center, but not specifically among neonates who received the prophylaxis. Our observations about anti-fungal resistance and reduction in *Candida* infections are also limited by the fact that species identification had been performed in only 58% isolates. Also, being retrospective, the interventions were not blinded and collateral data about details of bacterial sepsis, NEC, month-wise break-up, clinical symptoms and adverse effects could not be accurately retrieved.

We conclude that the usage of prophylactic Fluconazole decreased the incidence of fungal sepsis despite several risk factors of fungal sepsis increasing over time. With Fluconazole prophylaxis, the onset of fungal sepsis was delayed by a mean duration of around 6 days. Cessation of the fungal

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prophylaxis policy did not result in a resurgence of fungal sepsis. Larger, prospective studies are required to further investigate these issues.

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