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Original Article

A Quality Improvement Initiative To Reduce Invasive Candidiasis In Extremely Low Birth Weight Neonates

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ABSTRACT

Objective: To evaluate the impact of a quality improvement (QI) initiative, which included a Fluconazole prophylaxis protocol and provider education on neonatal Candidiasis.

Study Design: Retrospective longitudinal study.

Place and Duration of Study: Neonatal Intensive Care Unit (NICU), Aga Khan University, Karachi Pakistan, from Apr 2015 to Dec 2019.

Methodology: All extremely low birth weight neonates (ELBW) neonates admitted to the NICU between April 2015 and March 2017 were included in the pre-implementation phase. All ELBW neonates admitted between April 2017 and December 2019 were included in the post-implementation phase. Data were collected from medical records. The primary outcome was the frequency of Invasive Candidiasis (IC) before and after the QI initiative.

Results: Altogether, 272 neonates were included in the study, with 115 neonates in the Pre-Implementation Group and 157 neonates in the Post-Implementation Group. The frequency of IC was 6(5.2%) in the pre-implementation and 1(0.6%) in the post-implementation period, (p=0.044). *Candida parapsilosis* 2(40%) and *Candida glabrata* 2(40%) were the organisms most commonly isolated from blood cultures. All organisms were sensitive to Fluconazole in both the pre-and post-implementation cohorts. There was no difference in mortality (54(50.5%) vs. 69(44.2%), p=0.32) or length of stay (19.6±13.3 vs. 23.4±18.4 days, p=0.061) before and after Fluconazole prophylaxis.

Conclusion: The frequency of invasive *Candidiasis* in ELBW neonates was successfully reduced by introducing a Fluconazole prophylaxis protocol in the NICU as a QI initiative. A team-based approach and provider education ensured high compliance.

Keywords: Candidiasis, Antifungal agents, Intensive care units, Infant, Newborn, Very low birth weight, Length of stay

How to Cite This Article: *Saleem SM, Jiwani U, Hussain AS, Kumar M, Kumar RS, Ariff S. A Quality Improvement Initiative To Reduce Invasive Candidiasis In Extremely Low Birth Weight Neonates. Pak Armed Forces Med J 2024; 74(1): 168-173.*

DOI: https://doi.org/10.51253/pafmj.v74i1.9446

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INTRODUCTION

Invasive Candidiasis (IC) is associated with significant morbidity, mortality, and hospital costs in very low birth weight (VLBW) and extremely low birth weight (ELBW) neonates. Among ELBW neonates, IC is associated with substantial mortality, ranging from 26% to 57%.[1,2] More than half the survivors have impaired neurodevelopment despite treatment with antifungal agents.[3]

Individual neonatal intensive care units (NICUs) have reported IC cases ranging between 3% and 23%, depending on the complexity of the unit.[4] The risk of IC increases with decreasing birth weight, with neonates weighing less than 750g having the highest risk of acquiring systemic infections.[5] An immature immune response, compromised skin and mucosal barriers, frequent use of invasive devices such as mechanical ventilation and central venous catheters, and prolonged use of parenteral nutrition and broad-spectrum antibiotics contribute to the increased risk of IC in VLBW and ELBW neonates.[6] In addition, the mode of delivery and horizontal transmission through healthcare workers are also considered risk factors for IC.[7]

Primary prevention strategies for IC include reducing exposure to modifiable risk factors by complying with hand hygiene standards, minimizing the use of invasive devices, practising antibiotic stewardship, and administering prophylactic anti-fungal agents.[8] Prophylactic Fluconazole therapy has been shown to reduce the colonization of the skin, gastrointestinal, and respiratory tracts.[9] Moreover, previous studies have demonstrated that compared to placebo, Fluconazole prophylaxis decreases the rates of IC in VLBW and ELBW neonates.[10]

Nearly half of the infections occurred in neonates with birthweight <1500g, and *Candida albicans* was reported as the leading causative organism (55%).[8] Since then, the NICU has expanded, and ELBW admissions in the unit have doubled. Given the

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Received: 03 Nov 2022; revision received: 19 Dec 2022; accepted: 26 Dec 2022

potential benefits of antifungal prophylaxis and the morbidity, mortality, and healthcare costs associated with IC, we undertook a quality improvement initiative by introducing a Fluconazole prophylaxis protocol and provider education in our NICU. We conducted a retrospective longitudinal study to report the outcomes of our quality improvement initiative.

METHODOLOGY

The retrospective longitudinal study was conducted at the Level III NICU, Aga Khan University Hospital, Karachi, Pakistan, from April 2015 to December 2019 approval from the Ethical Review Committee was taken (2022-7500-21806). The sample size was estimated using Open Epi software, taking a percentage of unexposed with the outcome as 16%, and an odds ratio of 0.314.[11]

Inclusion Criteria: Neonates of either gender with a birth weight <1000g admitted to the Aga Khan University NICU were included.

Exclusion Criteria: All neonates with a birth weight ≥1000g were excluded.

The unit has four bays with five cots each, placed six feet apart, and four isolation rooms. Approximately 1200 neonates are admitted to the NICU every year, including neonates born in the hospital and those referred from other centres. The nurse-to-patient ratio is 1:1 for neonates with culture-proven infections and 1:2 for other neonates. Post-graduate medical trainees, including pediatric residents and NICU fellows, are routinely involved in patient care. Our hospital has established protocols to reduce the risk of invasive fungal infections, including eliminating routine suctioning of neonates, protocols for appropriate hand hygiene, central venous catheter (CVC) insertion, and CVC maintenance practices. The primary team discusses discontinuing central lines and antibiotic therapy daily. Parenteral nutrition is prepared with aseptic technique in the hospital pharmacy.

The decision to initiate prophylactic Fluconazole for ELBW neonates was based on scientific evidence and accumulated experience. Over several meetings, NICU providers, including neonatologists, NICU fellows, and the head nurse, reviewed the current evidence, guidelines, and personal communications with neonatologists on Fluconazole prophylaxis at different centres. Given the highly variable prevalence of IC in our unit, the frequent presence of risk factors of IC in our population includes the almost universal use of broad-spectrum antibiotics and central lines. Given the substantial evidence of Fluconazole prophylaxis's effectiveness, a consensus was developed to initiate a prophylactic Fluconazole protocol in the unit.

The pre-implementation phase started from 1st April 2015 to 31st March 2017. Data were retrieved retrospectively from patient records at the study institute's Health Management Information System (HIMS) department.The protocol was initiated in April 2017, following which each ELBW neonate in the unit was administered 6 mg/kg Fluconazole every 72 hours for four weeks. During the first week of the implementation, the on-call neonatologist placed the order for Fluconazole for each new ELBW admission. The NICU fellows and head nurse ensured that all ELBW neonates received the subsequent doses of Fluconazole every third day according to the protocol. In the same week, the daily morning patient rounds incorporated education sessions for NICU residents and fellows on the rationale, dose, and duration of Fluconazole prophylaxis. A similar orientation to the protocol was included in the daily in-service training sessions for the nursing staff. Prophylactic Fluconazole was discontinued for proven or presumed invasive fungal infections, and empirical systemic antifungal therapy was initiated.

Data were retrieved retrospectively from patient records for all ELBW neonates admitted to the NICU from 1st April 2015 to 31st March December 2019.

The primary outcome was the frequency of IC in ELBW neonates. Secondary outcomes included mean length of stay and mortality. IC was defined as the presence of Candida spp. in the bloodstream, cerebrospinal fluid, or urine collected by sterile bladder catheterization or sterile suprapubic puncture, with growth of 10,000 fungal organisms/mL.[12,13]

Medical data collected from HIMS were imported to Stata version 12 for statistical analysis. Frequencies and percentages were reported for categorical variables. Mean±SD were reported for continuous variables depending upon data distribution. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using unpaired t-tes. The *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 272 neonates were included in the study, with 115(42.3%) in the Pre-Implementation Group and 157(57.7%) in the Post-Implementation

Group. Table-I presents the demographic and clinical characteristics of the Pre-Implementation and Post-Implementation neonates.

The neonates in the Pre-Implementation Group had a higher frequency of pre-labour rupture of membranes (27(23.5%) vs. 15(9.6%), p=0.002) than the Post-Implementation Group. The mean duration of antibiotic use (3.8 vs. 5.1 days, p=0.004) and mechanical ventilation (6.6 vs. 8.7 days, p=0.028) were shorter in pre-implementation neonates. Using proton pump inhibitors (PPIs) or H2 blockers (44(38.9%) vs 40 (25.6%), p=0.02) was more common in the pre-implementation cohort. Almost all neonates in the pre-implementation group 108 (93.9%) had a central venous catheter in place compared to 125(73.6%) of the post-implementation neonates, p<0.001.

There was no difference in mortality 54 (50.5%) vs. 69(44.2%), p=0.32) or length of stay (13.3 vs. 18.4 days, p=0.061) before and after Fluconazole prophylaxis.

Six neonates (5.2%) in the pre-implementation period and one neonate (0.6%) in the post-implementation period acquired IC (p=0.044) (Table-II). The only case of IC in the post-implementation period was found in a neonate who was readmitted to the NICU on the 24th day of life. *Candida parapsilosis* 2 (40%) and *Candida glabrata* 2 (40%) were the organisms most isolated from blood cultures. *Candida albicans* was only isolated from the urine cultures. All isolated organisms were sensitive to Fluconazole in pre- and post-implementation neonates.

Table-I: Demographic and Clinical Characteristics of Pre- and Post-Intervention Neonates (n=272)

	Pre-Implementation (n=115)	Post-Implementation (n=157)	Total (n=272)	*p*-value
Gestational age in weeks, Mean±SD	27.8±2.6	27.6±2.2	27.7±2.4	0.49
Birth weight in kg, Mean±SD	0.8±0.2	0.8±0.2	0.8±0.2	0.12
Gender, n (%)				0.71
Male	61(53.0%)	79(50.3%)	140(51.5%)	
Female	54(47.0%)	78(49.7%)	132(48.5%)	
Mode of delivery*, n (%)				0.064
EM-LSCS	82(71.3%)	124(79.0%)	206(75.7%)	
SVD	30(26.1%)	33(21.0%)	63(23.2%)	
LSCS	3(2.6%)	0(0.0%)	3(1.1%)	
PROM >18 hours, n (%)	27(23.5%)	15(9.6%)	42(15.4%)	0.002
Use of broad-spectrum antibiotics*, n (%)				0.37
Ampicillin + gentamicin	108(93.9%)	150(95.5%)	258(94.9%)	
Cefotaxime + amikacin	7(6.1%)	5(3.2%)	12(4.4%)	
Meropenem + vancomycin	0(0.0%)	2(1.3%)	2(0.7%)	
Duration of antibiotic therapy, mean±SD	3.8±3.5	5.1±3.7	4.6±3.7	0.004
Central line use, n (%)	108(93.9%)	125(79.6%)	233(85.7%)	<0.001
Duration of central line, mean±SD	12.6±8.9	15.5±10.3	14.1±9.8	0.024
Use of TPN*, n (%)	111(96.5%)	150(95.5%)	261(96.0%)	0.76
Use of proton pump inhibitors/H2 blockers, n (%)	44(38.9%)	40(25.6%)	84(31.2%)	0.020
Necrotizing enterocolitis, n (%)	28(24.3%)	33 (21.0%)	61(22.4%)	0.52
Non-fungal sepsis**, n (%)	59(51.3%)	120(76.4%)	179(65.8%)	<0.001
Mechanical ventilation, n (%)	93(80.9%)	126(80.3%)	219(80.5%)	0.90
Duration of mechanical ventilation, mean±SD	6.6±6.5	8.7±7.7	7.8±7.3	0.028
Length of stay in days, mean±SD	19.6±13.3	23.4±18.4	21.8±16.5	0.061
Blood transfusion, n (%)	77(67.0%)	98(62.4%)	175(64.3%)	0.44
Death, n (%)	54(50.5%)	69(44.2%)	123(46.8%)	0.32

** reported fisher's exact test of association*

*** culture proven and clinical sepsis*

EM-LSCS: emergency lower segment cesarean section; SVD: spontaneous vaginal delivery; PROM: prelabor rupture of membranes; TPN: total parenteral nutrition

Table-II: Invasive Candidiasis in Study Neonates (n=272)

	Pre-implementation (n=115)	Post-implementation (n=157)	Total (n=272)	*p*-value
Invasive Candidiasis	6 (5.2%)	1 (0.6%)	7 (2.6%)	0.044
Organisms isolated from blood culture, n (%)				1.00
Candida parapsilosis	2 (50%)	0 (0.0%)	2 (40%)	
Candida glabrata	1 (25%)	1 (100%)	2 (40%)	
Candida tropicalis	1 (25%)	0 (0.0%)	1 (20%)	
Organisms isolated from urine culture, n (%)				
Candida albicans	2 (100%)	--	2 (100%)	
Sensitivity to Fluconazole, n (%)	6 (100%)	1 (100%)	7 (100%)	--
Sensitivity to voriconazole, n (%)	5 (83%)	1 (100%)	6 (86%)	1.00
Sensitivity to amphotericin B, n (%)	1 (17%)	1 (100%)	2 (29%)	0.29
IC on day of life, Mean±SD	22.7±32.3	24.0	22.9±29.4	0.97
IC on day of NICU stay, Mean±SD	7.7±5.6	24.0	10.0±8.0	0.042

**Fisher's exact test of association*
IC: invasive Candidiasis

Table-III: Factors associated with Invasive Candidiasis (n=272)

	Neonates withoutIC(n=265)	Neonates with IC(n=7)	Total (n=272)	*p*-value*
Gestational age in weeks, Mean±SD	27.7±2.4	28.1±1.8	27.7±2.4	0.63
Birth weight in kg, Mean±SD	0.8±0.2	0.8±0.1	0.8±0.2	0.55
Gender, n (%)				0.45
Male	135(50.9%)	5(71.4%)	140(51.5%)	
Female	130 (49.1%)	2(28.6%)	132(48.5%)	
Mode of delivery, n (%)				0.056
EM-LSCS	202(76.2%)	4(57.1%)	206(75.7%)	
SVD	61(23.0%)	2(28.6%)	63(23.2%)	
LSCS	2(0.8%)	1(14.3%)	3(1.1%)	
PROM >18 hours, n (%)	41(15.5%)	1(14.3%)	42(15.4%)	1.00
Use of broad-spectrum antibiotics, n (%)				0.31
Ampicillin + gentamicin	252(95.1%)	6(85.7%)	258(94.9%)	
Cefotaxime + amikacin	11(4.2%)	1(14.3%)	12(4.4%)	
Meropenem + vancomycin	2(0.8%)	0(0.0%)	2(0.7%)	
Duration of antibiotic therapy, mean±SD	4.5±3.6	4.9±4.2	4.6±3.7	0.83
Central line use, n (%)	227(85.7%)	6(85.7%)	233(85.7%)	1.00
Duration of central line, Mean±SD	14.3±9.8	10.2±6.5	14.1±9.8	0.31
Use of TPN, n (%)	255(96.2%)	6(85.7%)	261(96.0%)	0.25
Proton pump inhibitor/H2 blocker, n (%)	82(31.3%)	2(28.6%)	84(31.2%)	1.00
Necrotizing enterocolitis, n (%)	59(22.3%)	2(28.6%)	61(22.4%)	0.66
Non-fungal sepsis, n (%)	173(65.3%)	6(85.7%)	179(65.8%)	0.43
Mechanical ventilation, n (%)	215(81.1%)	4(57.1%)	219(80.5%)	0.14
Duration of mechanical ventilation in days, Mean±SD	7.7±7.3	9.8±4.6	7.8±7.3	0.58
Length of stay in days, Mean±SD	21.8±16.7	20.7± 11.0	21.8±16.5	0.86
Blood transfusion, n (%)	170(64.2%)	5(71.4%)	175(64.3%)	1.00
Death, n (%)	118(46.1%)	5(71.4%)	123(46.8%)	0.26

**Fisher's exact test of association*
IC: invasive Candidiasis; EM-LSCS: emergency lower segment cesarean section; SVD: spontaneous vaginal delivery; PROM: prelabor rupture of membranes; TPN: total parenteral nutrition

Table-III presents the factors associated with IC. There were no significant differences between neonates with and without IC. All neonates in the study received broad-spectrum antibiotics. Mortality was lower in the neonates who did not have IC compared to neonates with IC, but the difference was not statistically significant (118(46.1%) vs. 5(71.4%), p=0.26). The mean duration of hospital stay was

similar between the two groups (21.8 vs. 20.7 days, p=0.86).

DISCUSSION

This quality improvement initiative aimed to introduce a Fluconazole prophylaxis protocol in the NICU using a team-based approach. Following the implementation of the protocol, the prevalence of IC in ELBW neonates declined from 5.2% to 0.6%. Several studies have reported a decrease in the incidence of IC following Fluconazole prophylaxis.[14] A meta-analysis using patient-level data from randomized trials demonstrated that Fluconazole prophylaxis reduced the odds of IC by 80% in preterm neonates without increasing the risk of adverse events or emergence of resistant species.[10]

Despite a reduction in IC cases, prophylactic Fluconazole did not demonstrate a mortality benefit in our unit. These results are consistent with some studies.[15,16] but not all studies.[17,18] A meta-analysis of randomized controlled trials and cohort studies reported that Fluconazole prophylaxis was associated with reducing IC-associated mortality.[19] However, this effect was driven by studies that used more frequent Fluconazole doses than our protocol. These studies continued Fluconazole prophylaxis for six weeks, increasing the frequency of the drug from every third day in the first two weeks to every second day in the next two weeks and every day in weeks five and six.[20] Although we did not observe a mortality benefit, a reduction in IC alone may be clinically meaningful.

We did not find a shift towards infections with Fluconazole-resistant Candida species after implementing the antifungal prophylaxis protocol. A multi-centre study that collected data over five years after initiating Fluconazole prophylaxis did not report an increase in the proportion of resistant species in fungal isolates.[17]

All ELBW neonates in the study received prophylactic Fluconazole in the post-implementation phase. The high level of compliance was likely due to our team approach, where we first reached a consensus about the protocol before initiating it in the NICU. We had multiple meetings where available literature, international guidelines, and personal communications with providers at other centres were reviewed. We decided to initiate our protocol due to the additional risk factors of IC found in our population, such as lack of antimicrobial stewardship, frequent use of central lines, and high rates of candida growth in bloodstream infections.

The second step in our initiative involved working with bedside providers to ensure adherence to the protocol. We included Fluconazole prophylaxis in the in-training education sessions for nurses and teaching rounds for residents to explain our goal of reducing IC in our unit. This strategy was important because pediatric residents and NICU fellows are often the first healthcare providers to encounter new patients and initiate care. Moreover, at least one neonatal fellow is always present in the NICU. Because of this reason, we designated the neonatal fellows to ensure that all ELBW neonates were receiving Fluconazole according to the schedule. This team approach led to a hundred per cent compliance with the antifungal prophylaxis protocol.

LIMITATIONS OF STUDY

This study has some limitations. The data for the study were collected retrospectively and from a single institute, which may limit the generalizability of the study. However, the NICU in our hospital has a high influx of referral cases from all over the city. Additionally, due to the small number of cases of IC, we could not adjust the known risk factors of IC in a multivariate model.

CONCLUSION

The frequency of invasive Candidiasis in ELBW neonates was successfully reduced by introducing a Fluconazole prophylaxis protocol in the NICU as a quality improvement initiative. A team-based approach and provider education ensured high compliance.

ACKNOWLEDGEMENTS

We are grateful to Javeriah Khan, Nobel Joseph, and Uzair Ansari.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

SMS & UJ: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

ASH & MK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

RSK & SA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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