

Candida Enfeksiyonlarında Probiyotik: Tek Merkez Yenidoğan Yoğun Bakım Ünitesinde On Yıllık Tecrübe
Probiotics in Candida Infections: Ten Years Experience in Single Neonatal Intensive Care Unit

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Özet

Amaç: Candida türleri, yenidoğan popülasyonunda en önemli morbidite ve mortalite nedenlerinden biridir. Yenidoğanlarda kandida enfeksiyonlarında probiyotik kullanımı tartışmalıdır. Bu çalışmanın amacı yenidoğan yoğun bakım ünitesinde kandida enfeksiyonlarını değerlendirmektir.

Metod: YYBÜ'de Candida enfeksiyonu için risk faktörlerini belirlemek için retrospektif tek merkezli, karşılaştırmalı bir vaka kontrol çalışması tasarlanmıştır. Çalışmaya alınan hastaların tümü, çalışma süresi boyunca en az 72 saat YYBÜ'de bulunan yenidoğanlardı. Her vaka için negatif kan kültürü olan 2 kontrol vakası 3 faktör açısından eşleştirildi: gebelik yaşı, doğum ağırlığı, hastanede kalış süresi (1 hafta içinde).

Sonuç: 7696 yenidoğan on bir yıl boyunca YYBÜ'de 72 saatten fazla yatırıldı ve 51 vaka (% 0,66) kandida enfeksiyonu ile takip edildi. Kontrol grubunda probiyotik kullanımı daha yüksekti. Cerrahi müdahaleler, santral venöz hatlar ve parenteral beslenme süresi, çoklu antibiyotik kullanımları kandida enfeksiyonları için risk faktörleri olarak bulundu.

Sonuç: YYBÜ'de kandida enfeksiyonlarının insidansını azaltmak için çoklu antibiyotiklerin genel kullanımını azaltmanın yanı sıra probiyotik kullanımını artırmaya, kateter bakımını iyileştirmeye etkin bir şekilde odaklanmalıyız. Probiyotiklerin Candida enfeksiyonlarına karşı koruyucu etkisi olabilir.

Anahtar Kelimeler: yenidoğan, kandida enfeksiyonu, risk faktörleri, probiyotikler

Abstract

Objectives: Candida species are one of the most important causes of morbidity and mortality in the neonatal population. The probiotic use is not well documented in candida infections in neonates. The aim of this study was to evaluate candida infections in neonatal intensive care unit.

Methods: A retrospective single-center, matched, case-control study was designed to identify individual risk factors for Candida infection in the NICU. Patients enrolled in the analysis were all neonates who were in the NICU during the study period for at least 72 h. For each case, 2 control cases with negative blood culture were matched on 3 factors: gestational age, birth weight, hospitalization time (within 1 week compared to case patients).

Results: 7696 newborns were admitted to and hospitalized >72 h in the NICU for eleven years and 51 cases (0.66 %) were followed with candida infection. Probiotic usage was higher in control group. Surgical interventions, central venous lines and parenteral nutrition duration, multiple antibiotic usages were found to be risk factors for candida infections.

Conclusion: In NICU we should effectively focus on increasing using of probiotics, besides decreasing the overall use of multiple antibiotics, improving catheter care to reduce the incidence of candida infections. Probiotics might have protective effect against candida infections.

Key Words: neonate, candida infection, risk factors, probiotics

Introduction

Fungal infections are serious health conditions that occur more frequently in vulnerable populations, such as in neonates

being cared for in the neonatal intensive care unit (NICU).^{1,2}In neonates, fungal infections are mostly from Candida, especially *Candida albicans* and, more recently, *Candida parapsilosis*.^{3,4}

Candidemia, one of the important causes of late-onset sepsis, is associated with significant morbidity and mortality.⁵The increased predisposition of neonates in the NICU to candida infections is due to their immature immune systems. The other predisposing factors associated with candidemia include prematurity, VLBW, vascular catheters, parenteral nutrition, administration of broad-spectrum antibiotics, administration corticosteroids and H2 inhibitors, surgery, prolonged hospitalization, and artificial ventilation.^{3,4,6,7}

The aims of the present study were to evaluate the incidence and epidemiology of candida infections in neonates and determine the risk factors and clinical outcomes associated with candida infections to select effective preventive measures and medical treatment for neonatal candida infections.

Methods

Çukurova University Balcalı Hospital NICU is a tertiary care level NICU with a total of 42 incubators. The ward serves the University Obstetric Clinic which is a perinatology center for both the high risk pregnancies and the obstetric emergencies. Moreover, the NICU admits outborn neonates from the regional hospitals. The tertiary-level NICU of Çukurova University Balcalı Hospital has approximately 750 admissions per year.

Fluconazole prophylaxis is started within the first 48 to 72 hours after birth at dose of 3 mg/kg per dose given intravenously twice a week for four to six weeks or until the

infant no longer requires intravenous access.⁸

A retrospective single-center, matched, case-control study was designed to identify individual risk factors for Candida bloodstream infection in the NICU. Patients enrolled in the analysis were all neonates who were in the NICU during the study period (January 2007–December 2017) for at least 72 h. Cases were neonates with clinical sign of neonatal sepsis and isolation of Candida species in the blood or urine cultures. For each case, 2 controls (negative blood culture) were matched on 3 factors: gestational age, birth weight, hospitalization time (within 1 week compared to case patient). Controls were all birth weight and gestational age, birth weight and hospitalization time matched neonates without candida isolation who were in the NICU for >72 h during the study period.

Approval was obtained from the institutional review board at University Ethical Committee. Data of the patients with infections were collected by an active surveillance system in the hospital and data of the patients were enrolled from this system.

An episode of candidemia was defined if an infant had a positive blood culture for candidemia.⁹

Central line or- umbilical catheter were recorded if a central line or an umbilical catheter were in place at the time of or within 7 days before infection onset.

Cases with isolation of candida <10.000 col/ml in tracheal aspirates without radiologic signs of pneumonia were excluded. Urinary tract infections were diagnosed if catheter collected urine culture were positive for candida.

Neonates with feeding intolerance were supported with probiotic; Bifidobacterium

lactis + Hindiba inulin. Feeding intolerance was diagnosed with at least two of the following criteria: 1) Less than 75 ml/kg/day enteral feeding at the end of the first postnatal week, 2) Gastric residuals (gastric aspirate more than 50% of previous feeding volume), 3) Emesis/Vomiting, 4) Abdominal distention (increase in abdominal girth), 5) Gastrointestinal bleeding.^{10,11} Each sachet containing Bifidobacterium lactis, 5X10⁹ colony forming units, 30 mg plus H Inulin, 900 mg (Maflor, Mamsel Pharmaceutical Company, İstanbul, Turkey) were diluted with 10 mL distilled water and 1 mL of this dilution was given three times a day to the infants for at least ten days. Each sachet was used within 24 hours after dilution.

The electronic records of newborns were screened, and the data were extracted as follows: birth weight, gestational age, admission age, gender, in/outborn, antenatal steroid, maternal diseases (e.g., urinary tract infection(UTI), choriamnionitis), type of delivery, fetal membrane rupture, respiratory distress syndrome, necrotizing enterocolitis, hypoxic ischemic encephalopathy, intraventricular hemorrhage, congenital heart disease, major congenital anomalies , surgery, mechanical ventilation, umbilical catheter, peripherally inserted central catheter (PICC), central venous catheter (CVC), urinary catheter, resuscitation history, H₂ blocker use, probiotic use in the last 7 days of infection, total parenteral nutrition duration, hospitalization duration, carbapenem use, vancomycin use, multiple antibiotic (≥ 3 types) use, prophylactic antifungal therapy, and outcome of candida infections.

Statistical analysis

Statistical analysis was conducted with SPSS 17.0 software (SPSS Inc, Chicago,

Illinois, USA). The chi-square test was used for comparisons of categorical variables. The t-test was performed to compare two group means. For non-normally distributed variables the Mann–Whitney test was performed. P values less or equal to 0.05 were accepted as statistically significant

Results

8515 newborns were admitted to the NICU from January 2007 to December 2017 and 7696 neonates were hospitalized >72 h. 51 cases (0.66 %) were followed with candida infection in eleven years.

The mean gestational age and mean birth weight of the candida (+) group were 32.6±5.3 (25-42) weeks and 2054.9±1822 (585-5370) g, respectively. 13 (25.5%) patients were ELBW (birth weight <1000 gr) and 8 cases (15.7%) were between 1000-1500 gr birth weight in candida (+) group. 24 cases (47.1%) were male and 13 (25.5%) were born via vaginally in candida (+) group. 35 cases (68.6%) were inborn. 17 (33.3%) neonates had non cardiac congenital anomalies while 12(23.5%) had congenital cardiac anomalies in candida (+) group.

The mean gestational age and mean birth weight of the control group were 33.2±4.6 (24-42) weeks and 2127.9±1840 (700-4460) g, respectively. 22 (22%) patients were ELBW (birth weight <1000 gr) and 18 cases (18%) were between 1000-1500 gr birth weight in control group. 57 cases (57%) were male and 26 (26%) were born via vaginally in control group. 93 cases (93%) were inborn. 14 (14%) neonates had non cardiac congenital anomalies while 12(12%) had congenital cardiac anomalies in control group.

Candida infections were diagnosed at 35.41±36.7 (1-176) days of hospitalization. Only one inborn patient with congenital heart defects whose mother had candida (+) amniotic fluid, had candidemia at postnatal first day of life. 47(92.2%) neonates had blood stream infection (BSI) while 4 (7.8%) had positive urinary culture. Three cases of the urinary tract infection had neurogenic urinary bladder, and one had severe hydronephrosis.

20 neonates had (39.2%) *C albicans*, 8 cases had (15.6%) *C parapsilosis*, 23 cases had (45.1%) *nonalbicans* Candida.

Table 1. Demographic properties of the neonates

	Candida (+) N= 51	Control N= 100	p
	Mean± SD Min-Max	Mean± SD Min-Max	
Gestational week (wk)	32.63±5.3 25-42	33.18±4.61 24-42	0.454
Birth Weight(gr)	2054.88±1822 585-5370	2127.88±1840 700-4460	0.338
Admission age (days)	4,1±7,90 0-38	0.2±0.99 0-8	<0.001
TPN duration(days)	45.88±33.36 10-150	13.89±14.14 0-57	<0.001
Hospitalization Duration(day)	81.41±64.87 9-380	36.93±21.68 3-86	<0.001
	N (%)	N (%)	
Preterm/term	38/13	73/27	0.752
Gender; male	24	57	0.162
Inborn	35 (68.6%)	93(93%)	<0.0001

Vaginal birth	13 (25.5%)	26 (26%)	0.555
Antenatal steroid(+)	17 (33.3%)	24 (24%)	0.152
UTI of mother	11(21.6%)	47 (47%)	0.002
Chorioamnionitis (+)	1(2%)	0	0.338
RDS	22(43.1%)	29(29%)	0.061
HIE	0	2(2%)	0.437
NEC	3(5.9%)	2(2%)	0.213
IVH	8(15.7%)	28(28%)	0.045
Congenital heart defects (CHD)	12(23.5%)	12(12%)	0.057
Congenital anomaly other than CHD	17(33.3%)	14(14%)	0.006
Mechanical ventilation(+)	33(64.7%)	65(65%)	0.378
Surgery	28 ⁺⁺ (54.9%)	12(12%)	<0.001
Umbilical catheter(+)	6 (11.8%)	49 (49%)	<0.001
PICC line(+)	15(29.4%)	17(17%)	0.062
CVC(+)	21(41.2%)	0	<0.0001
Probiotic use	3(5.9%)	50(50%)	<0.001
Antifungal Prophylaxis	1 (2%)	10 (10%)	0.064
Multiple AB use	46(90.2%)	74(74%)	0.006
Vancomycin use	36(70.6%)	38(38%)	<0.0001
Carbapenem use	34(66.7%)	40 (40%)	0.001
H ₂ blocker use	12(23.5%)	35(35%)	0.104
Thorax tube(+)	12(23.5%)	7 (7%)	0.005
Urinary catheter>4 days	7(13.7%)	0	<0.05
Exitus	16(31.4%)	5(5%)	<0.0001

⁺⁺: either abdominal or cardiac surgery in last 3 days of diagnosis of candida infection, UTI: Urinary Tract Infection, RDS: respiratory distress syndrome, NEC: necrotizing enterocolitis, HIE: hypoxic ischemic encephalopathy, IVH: intraventricular hemorrhage, PICC: peripherally inserted central catheter, CVC: central venous catheter,

In control group none of neonates had central venous catheters ($p<0.0001$), 49 (49 %) cases had umbilical catheters ($p<0.001$), 17 (17%) cases had peripherally inserted central catheters ($p=0.062$), and none of the neonates had urinary catheters longer than 4 days.

Only one patient had prophylactic antifungal treatment before the diagnosis of candidemia in candida (+) group while 10 neonates (10%) had prophylactic antifungal treatment ($p=0.064$). The overall mortality rate in the candida (+) group was 31.4%, while the mortality rate in the control group was 5%. ($p<0.0001$).

Discussion

Invasive fungal infections (IFI) are important infections in NICUs, with Candida BSI being the most common IFI.¹² More than 80% of the Candida BSIs were seen in neonates with birth weight of <1500

g.^{13,14} Apart from birth weight, there are several other risk factors associated with Candida infections in neonates.

Birth weight and gestational age are the most important risk factors both for developing candida infection and for associated mortality.¹⁵ In our study control group is case matched neonates, so that birth weight and gestational week was not different between controls and candida group. We aimed to compare risk factors other than birth weight and gestational week for candida infections.

Admission age was significantly higher in candida group. Our university is a center for many health disciplines like neonatal cardiac surgery, metabolism, pediatric surgery and interventions for premature retinopathy. We transfer many babies from other centers. We got blood culture at the first day of admission.

Candida species have capacity to attach to foreign materials (such as invasive and indwelling devices) and form biofilms, which may act as a biological barrier that prevents the penetration of antifungal agents. So that invasive and indwelling medical devices have been identified as factors associated with increased risk of candidemia.¹⁶

Central venous catheterization and total parenteral nutrition were identified as significant predisposing factors for the development of candidemia in our study. The majority of the infected neonates had received central venous catheterization (41,2%) and longer total parenteral nutrition ($p<0,001$). Although in some studies, umbilical catheterization is also a risk factor for candida infection, in our study it was not a risk factor.

Surgery in neonatal period is also a major risk factor. Yu et al reported that surgeries could be a risk factor for neonatal candidemia.⁹ Also Liu et al reported that surgery appeared to be the risk factors of candidemia in neonates and in our study either cardiac or abdominal surgery was statistically significant in candida(+) group.¹⁷

Both the European Society of Clinical Microbiology and Infectious Diseases and the Infectious Diseases Society of America recommend the use of fluconazole in doses varying from 3 to 6 mg/kg.^{18,19} Antifungal prophylaxis, was not statistically different between control and candida groups in our study. Prophylaxis for candida BSI is recommended not only to avoid death, but also to decrease neurocognitive and neurosensory sequelae.^{2,20}

Many investigations reported that use of broad spectrum antibiotics and prolonged antibiotic duration were common

risk factors associated with candidemia.^{2,21} The long term use of these broad-spectrum antibiotics in routine empirical therapy may lead to the overgrowth of opportunistic²² In our department, the majority of candidemia cases had received broad-spectrum antibiotics, such as vancomycine (70.6%) and carbapenems (66.7%), and 90.2% of patients received multiple antibiotics.

Probiotics, defined as live microorganisms, confer health benefits to a host when administered at adequate doses.²³ The exact mechanisms of how probiotics improve the health of the hosts are not clear. Substantial reports indicate that probiotics can reduce Candida colonization and IFIs in mice model.^{24,25} In NICU, intestinal functional immaturity, broad-spectrum antibiotics, and delay in initiating enteral feeding prevent the enteric colonization with normal commensal microorganisms.²⁶

Limited data support that probiotic supplementation prevents invasive fungal sepsis in preterm neonates. The safety and efficacy of probiotics in preterms especially ELBW is still controversial. In our study probiotic use was statistically higher in control group. Probiotics seem to be protective against candida infections in this study.

The use of post-natal steroids and H₂ inhibitors are factors that favor translocation in the colonized patient to invasive infection. In our study H₂ blocker use was not different between groups ($p=0,10$).

The mortality rate reported in some studies is around 20%, but it can reach up to 40%.^{27,28} In our study mortality rate was 31.4% in the candida (+) group and significantly higher than the control patients ($p<0,0001$).

Candida albicans is the most prevalent fungal pathogen in neonatal disease, but the incidence of infection caused by other *Candida* species has also increased dramatically and in the literature, the most prevalent *Candida* species causing candidemia has shifted over time from *albicans* to non-*albicans* species.^{29,30} Also in our study, *Candida nonalbicans* other than *C parapsilosis* was the most common pathogens (45,1%) while incidence of *C albicans* was 39.2%.

The limitations of the current study were its retrospective nature and single center design with small sample size.

As a conclusion, the local neonatal intensive care unit management teams should effectively focus on increasing using of probiotics in addition to decrease other risk factors to reduce the incidence of candidemia.

The authors have no conflicts of interest relevant to this article.

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