The Turkish Journal of Pediatrics 2017; 59: 20-27
DOI: 10.24953/turkjped.2017.01.004

Original

The effects of routine administration of probiotics on the length of central venous line usage in extremely premature infants

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Received: 26th September 2016, Revised: 12th January 2017, Accepted: 16th March 2017

SUMMARY: Rajput N, Filipovska J, Hewson M. The effects of routine administration of probiotics on the length of central venous line usage in extremely premature infants. Turk J Pediatr 2017; 59: 20-27.

The objective of this study was to determine whether the routine use of probiotics was associated with earlier removal of peripherally inserted central catheter (PICC) lines in extremely premature infants born ≤28 weeks' gestation.

This study was a retrospective, observational, cohort study in infants born ≤28 weeks gestation in the 2 years before [No Probiotic Group (NPG)] and after [Probiotic Group (PG)] the commencement of the routine use of probiotics (Infloran®) in a large tertiary neonatal intensive care unit in the North Island of New Zealand. Age at the removal of PICC line in patients whose first PICC lines were inserted before day 14 and remained in-situ for at least 4 days was compared using Kaplan-Meir Survival Analysis on SPSS 22.0®. We studied PICC line infections as a secondary outcome measure.

We compared 120 PICC lines in NPG and 130 PICC lines in PG. Mean age at removal was 25.9 [(95% Confidence Intervals (CI)=22.6 – 29.2)] days in NPG and 23.1 (95% CI=20.9 – 25.2) days in PG. The result was independent of birth weight, gender, type of PICC line and age at insertion but related significantly to gestation at birth (p<0.001). There was no difference in the incidence or the microbiologic profile of PICC line infections between the study groups.

PICC lines were removed 2.8 days earlier in infants receiving probiotics (p=0.070), which can have potential benefits with reduced infection and other risks due to earlier removal of PICC lines.

Key words: probiotics, enteral nutrition, PICC line removal, necrotizing enterocolitis.

Probiotics in preterm infants – research evidence and safety

Results of a recent meta-analysis of 20 randomized controlled trials confirm that probiotic supplementation significantly reduces the risk of definite (i.e., Bell Stage 2 or higher[1]) necrotizing enterocolitis (NEC) [Relative risk = R 0.33; 95% Confidence Intervals (CI) = 0.24-0.46; p < 0.0001] and all-cause mortality (Relative risk = 0.56; 95% CI = 0.43-0.73; p < 0.0001) without any significant adverse effects in preterm very low birth weight infants[2]. The effect of probiotics on preterm gut is mediated through multiple mechanisms including decrease in intestinal bacterial colonization[3], increase in intestinal blood flow[4], improved balance of gut microbial ecology, strengthening of mucosal barrier function[5], modification of host response to microbial products, augmentation of immunoglobulin A mucosal responses, enhancement of enteral nutrition to inhibit the growth of pathogens, production of antimicrobial proteins, and competitive exclusion of potential pathogens[6].

Another large randomized trial (n = 999) has shown a reduction in late-onset sepsis in babies born ≥28 weeks gestation (p = 0.01) but not <28 weeks[7] as a result of probiotic administration. This trial showed a significant difference in weight at 28 days of life (p=0.04)

and a trend towards a difference in the length of initial hospital stay (p=0.09) and days to regain birth weight (p=0.06). There was no difference in mortality (except mortality due to NEC; p=0.07), duration of intravenous nutrition (IVN), days to full enteral feeds, breastfeeding rates, or weight at discharge. There was no reported difference in acute morbidities such as chronic lung disease, retinopathy of prematurity, intraventricular hemorrhage, and patent ductus arteriosus. In the long-term, there is no reported difference in growth and neurodevelopmental outcomes at ages three years[8] or 18 to 22 months[9].

Given the significant benefits of probiotics, our unit adopted the policy of routinely supplementing all infants born <34 weeks' gestation with Infloran ® (Bifidobacterium bifidum & Lactobacillus acidophilus) in December 2011. We aim to give Infloran in a dose of 250 mg daily as soon as the infants are tolerating enteral feeds of at least 1 ml every 2 hours and continue administration until 36 weeks' post-menstrual age. Each half-capsule of Infloran® capsules contains approximately 10^9 colony forming units.

Probiotics and Percutaneously Inserted Central Catheter (PICC Line) usage

We are unaware of any published study that has looked at the duration of PICC line usage in preterm babies receiving probiotics. Our primary aim was to assess retrospectively the age at the removal of PICC line in extremely premature infants born ≤28 weeks and receiving probiotics (Infloran®) as compared to the group not receiving Infloran®.

Material and Methods

The study was a retrospective, observational, cohort study based in a tertiary neonatal unit in New Zealand with approximately 800 admissions/year, nearly 5% of which are infants born ≤28 weeks' gestation.

The PICC line database

Our unit maintains a PICC line database for the purpose of infection surveillance with data on gestation, birth weight, date of birth, date of insertion and removal of PICC line and the reason for removal.

PICC line removal

All central lines including PICC lines are at risk for sepsis and other complications[10,11]. It is our unit policy to remove PICC lines within 24 hours of the infant reaching 150 ml/kg/day of enteral feeding.

Study Design

Infants born in the two years prior (No Probiotics Group; NPG) were compared with infants born

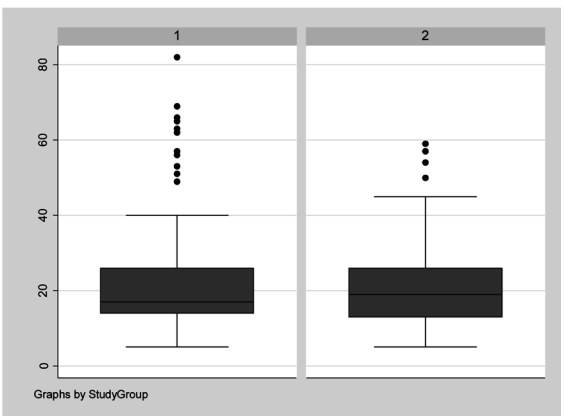

Fig. 1. Box-Plot of Age at Removal of PICC Line by Study Group (1-NPG, 2-PG)*
*(The two infants with proven NEC had their PICC line removed at 68 and 81 days of age respectively and are seen as outliers)
PICC: Peripherally-inserted central catheter, NEC: Necrotizing enterocolitis, NPG: No Probiotic Group, PG: Probiotic Group

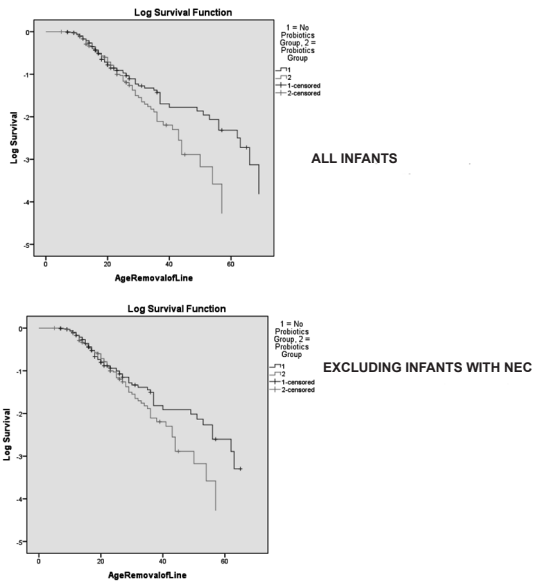

Fig. 2. Kaplan-Meir Log Survival Curves Comparing the Age at Removal of PICC line in No Probiotic and Probiotic Group

Table I. Comparison of Gestation, Gender, Birth Weight, Type of PICC Line, Age of Insertion and Removal and the Length of Time for which the PICC Line Remained in Situ for All First PICC Lines

	No Probiotic Group (NPG)		Probiotic Group (PG)	p-Value
	All infants (N=122)	Infants without Bell Stage 2 or higher NEC (N = 120)	(N=130)	[NPG (All infants) vs. PG]
Gestation in completed weeks [Median (IQR)]	26 (25-27)	25 (26-27)	26 (25-27)	0.4881
Number of Male Babies (Proportion of All Babies)	60 (49.2%)	59 (49.2%)	84 (64.6%)	0.0136*
Birth weight in grams [Mean (SD)]	922.5 (237.8)	926 (236.8)	905.1 (233.5)	0.5585
Number of Premicath PICC Lines [Proportion of All PICC Lines (95% Confidence Intervals)]	114 [93.4% (87.5 – 97.1)]	112 [93.3% (87.3 – 97.1)]	126 [96.9% (	0.1937
Number of PICC Lines removed as "No Longer Required" [Proportion of All PICC Lines (95% Confidence Intervals)]	92 [75.4% (67.8 – 83.1%)]	90 [75% (67.3 – 82.7%)]	112 [86.2% (80.2-92.1%)]	0.0291*
Age in Days at insertion of PICC Line [Median (IQR)]	1 (1-2)	1 (1-2)	1 (1-2)	0.8416
Duration in Days for which PICC line remained in situ [Median (IQR)]	15 (12-24)	12 (15-23.25)	17 (12-24)	0.5515
Age in Days at removal of PICC Line [Median (IQR)]	17 (14-26)	17 (13.75 – 25.25)	19 (13-26)	0.7195

*p<0.05 was considered significant. IQR = Interquartile range
PICC: Peripherally-inserted central catheter, NEC: necrotizing enterocolitis

in the two years after (Probiotics group; PG) the commencement of routine administration of probiotics. Our primary outcome measure was the age at PICC line removal when "no longer required". We analyzed catheter-related bloodstream infection in the two groups as a secondary outcome measure.

Inclusion Criteria

NPG – DOB – 01.12.2008 – 30.11.2011 (24 months).

PG – DOB – 01.01.2012 – 31.12.2013 (24 months).

Gestational age ≤28 completed weeks

PICC line insertion for the administration of IVN

Only first PICC lines inserted before Day14 of age

PICC line in situ for at least four calendar days

Exclusion Criteria

Infants with no PICC line insertion

All 2nd and subsequent PICC lines

PICC lines in situ for less than four calendar days or inserted after day 14 of age

Ethics approval

Ethics approval was not required because this study was purely observational using anonymized, retrospective data with no clinical intervention. We confirmed this with our Institutional Research Office and checked against the ethics approval criteria available from the website www.ethics.govt.nz.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows ®, version 22.0 (SPSS, Chicago, IL, USA). Kaplan-Meier Survival Curves were used to compare age at PICC line removal between NPG and PG. The endpoint for this analysis was the removal of PICC line when "No longer required". PICC lines removed for other reasons such as sepsis, malposition, obstruction, or extravasation were censored from the Kaplan-Meier analysis. Cox proportional hazards model was used to test the independent effects of gender, gestation, birth weight, the age of insertion of PICC line and type of PICC line (Premicath 1Fr vs. Epicath 2Fr). We repeated the analysis before and after excluding infants developing Bell Stage 2 or greater NEC (n=2) before removal of the 1st PICC line, to study potential delay in removal of PICC line due to the development of NEC. We analyzed demographic, and other data using student "t" test (for means and proportions) and Wilcoxon rank sum test (for medians in independent samples) and computed Inter-quartile ranges (IQR) and 95% CI as appropriate. We considered a p-value <0.05 as significant.

Results

Demographics

A total of 126 PICC lines were inserted in 122 infants in NPG (average = 1.03 PICC lines/ infant) and 139 PICC lines were inserted in 130 infants in PG (average = 1.08 PICC lines/ infant). Collective duration for which all PICC lines stayed in-situ was 2584 days in NPG and 2673 days in PG. Only 2 infants in NPG and none in PG developed Stage 2 or higher NEC before the removal of PICC line (Table 1). We did not find any differences between NPG and PG regarding gestation, birth weight,

Table II. Reasons for Removal of First – Inserted PICC Lines*

Reason for PICC line removal	No Probiotic Group (NPG)		Probiotic Group (PG) (N=130)	p-Value [NPG (All infants) vs. PG]
	All infants (N=122)	Infants without Bell Stage 2 or higher NEC (N = 120)		
No Longer Required (95% confidence intervals)	75.4% (66.8 – 82.7%)	75% (66.3 – 82.5%)	86.2% (79.0 – 91.6%)	0.0291†
Infection Concerns	13.1% (7.7 – 20.4%)	13.3% (7.8 – 20.7%)	6.9% (3.2 - 12.7%)	0.0996
Death	6.6% (2.9 – 12.5%)	6.7% (2.9 – 12.7%)	5.4% (2.2 – 10.8%)	0.6881
Transfer to Another Unit with PICC line in-situ	2.5% (0.5 – 7.0%)	2.5% (0.5 – 7.1%)	ZERO	Not analysed as these are technical reasons for removal of PICC line
Extravasation, Occlusion or Other Technical Reason	2.5% (0.5 – 7.0%)	2.5% (0.5 – 7.1%)	1.5% (0.19 – 5.4%)	
All Reasons for PICC line Removal	100.0%	100.0%	100.0%	-

*Parentheses indicate 95% confidence intervals. †indicates significant p-Value (< 0.05)
PICC: Peripherally-inserted central catheter, NEC: necrotizing enterocolitis

type of PICC line (Premicath vs. Epicath) and age at insertion (Table 1). There was a higher proportion of male infants in PG as compared to NPG.

Reasons for removal of PICC lines

The majority of PICC lines were removed when "no longer required" in PG (86.2%), relative to NPG (75.4%) (p=0.0291, where p<0.05 is significant). We have summarized the reasons for removal of PICC lines in Table II.

Age at removal of PICC lines

We report Medians and Inter-quartile ranges for duration the PICC lines stayed in-situ, and the age at removal in Table I. The median age of removal of PICC lines when "no longer required" was 18 (IQR=14 – 27 days) days in NPG and 19.5 (IQR=13 – 26.6; p=0.9610) days in PG.

Kaplan-Meir Survival Analysis

Analysis was performed using "removal when no longer required" as an endpoint, with censoring of all PICC lines removed for other reasons (Fig. 2). We report the Mean and Median age of removal of PICC lines between NPG and PG in Table III, both including and excluding infants with Bell Stage 2 or higher NEC. Mean age at the removal of PICC lines was 2.8 days earlier (with NEC infants excluded; p=0.186) or 4.1 days earlier (with NEC infants included; p=0.087) in PG as compared to NPG.

Cox Regression Analysis

Cox regression analysis for proportions was performed to assess the effect of other variables on the duration that PICC lines remained in-situ (Table IV). Infants born at younger

Table III. Kaplan-Meir Survival Analysis*

	No Probiotic Group (NPG)		Probiotic Group (PG) (N=130)
	All infants (N=122)	Infants without Bell Stage 2 or higher NEC (N = 120)	
Mean age in days at removal of PICC line	27.2 (23.5 – 30.9)	25.9 (22.6 – 29.2)	23.1 (20.9 – 25.2)
p-Value for difference in mean age at removal of PICC line	0.087	0.186	N/A

*95% confidence intervals in parentheses
PICC: Peripherally-inserted central catheter, NEC: necrotizing enterocolitis

Table IV. Cox Regression Analysis for Age at Removal of First PICC Line

	All infants in NPG vs. Infants in PG		Infants in NPG without Bell Stage 2 or higher NEC vs. Infants in PG	
Variable of interest	Hazard Ratio	p-Value	Hazard Ratio	p-Value
Birth weight	1.000 (0.999 – 1.001)	0.607	1.000 (0.999-1.001)	0.919
Infant Gender	0.897 (0.669 – 1.201)	0.464	0.913 (0.682 – 1.220)	0.537
Infant Gestation at birth	1.440 (1.256 – 1.651)	<0.001	1.486 (1.295 – 1.705)	<0.001
Type of PICC line – Premicath vs. Epicath	0.819 (0.353 – 1.900)	0.643	0.643 (0.322 – 1.736)	0.499
Age at Insertion	0.982 (0.900 – 1.071)	0.682	0.970 (0.887 – 1.061)	0.503
Study Group (PG vs. NPG – PG needing PICC lines for a shorter duration)	0.710 (0.532 – 0.947)	0.020	0.766 (0.574 – 1.022)	0.070

*Gestation is used as a continuous variable here
PICC: Peripherally-inserted central catheter, NEC: necrotizing enterocolitis, PG: Probiotic Group, NPG: No Probiotic Group

Table V. Organisms That Were Grown in Positive Blood Cultures*

	No Probiotic Group (NPG) (N = 28)	Probiotic Group (PG) (N = 44)	p Value
Coagulase Negative Staphylococcus	67.9% (47.6 – 84.1%)	79.5% (64.7 – 90.2%)	0.2679
Escherichia coli	17.9% (6.1 – 36.9%)	11.4% (3.8 – 24.6%)	0.4374
Staphylococcus aureus	7.1% (0.9 – 23.5%)	9.1% (2.5 – 21.7%)	0.7645
Acinetobacter	3.6% (0.09 – 18.3%)	Zero	0.2050
Other	3.6% (0.09 – 18.3%)	Zero	0.2050
Total	100.0%	100%	-

*95 percent confidence intervals in parentheses

gestations were older at the time of PICC line removal ($p<0.001$). There were no significant differences seen with regards to birth weight, gender, the type of PICC line and the age at insertion.

Sepsis Rates

A total of 28 positive blood cultures in 20 septic episodes were reported for 126 PICC lines in NPG. Meanwhile, 44 positive blood cultures in 24 septic episodes were recorded for 139 PICC lines in PG. This gave a septic episode rate of 7.7 (95% CI = 3.5 – 15.7) episodes per 1000 PICC line days in NPG and 7.5 (95% CI = 3.5 – 15.7) episodes per 1000 PICC line days in PG ($p = 0.9589$). We report the organisms grown in positive blood cultures in Table V, with Coagulase negative Staphylococcus being the commonest organism. While sepsis rates are similar, infection concerns were less common as a reason for removal of PICC line in PG as compared to NPG (Odds Ratio =2.0; $p=0.106$), as they were more likely to be removed for simply no longer being required in PG.

Discussion

This study provides useful insights into the effect probiotics might have on the age at the removal of PICC lines in extremely preterm infants born ≤28 weeks of gestation. PICC lines stayed in for 2.8 days (or 4.1 days when including infants with significant NEC) less in the Probiotic Group (PG) as compared to No Probiotic (NPG) group in this study. We did demonstrate a significant difference ($p = 0.020$) between the two groups on Cox regression analysis, although the difference was no longer statistically significant after we excluded two infants with significant NEC from NPG group ($p= 0.070$). There was no alteration in frequency or microbiological pattern of catheter-related PICC line infections in babies in the PG. PICC lines were more likely to be removed "when no longer required" in the PG.

The advantages of earlier removal of PICC lines include lesser risk of infections and hence less need for antibiotics with their attendant risks. There is also a reduced need for IVN and the avoidance of its adverse effects such as hepatotoxicity. Although the findings are no longer statistically significant after excluding babies with NEC, they are still clinically relevant and support the use of probiotics in extremely preterm infants. Using a larger sample size would have been helpful here but is unable to be generated due to our PICC line database only commencing in the latter part of the year 2008. We acknowledge that it is unlikely that a randomized, control trial will be approved by any ethics committee, given the significant protection against NEC from the administration of probiotics.

PICC lines could have been removed earlier because babies were reaching full enteral nutrition at an earlier age, although we were not able to study this directly due to lack of access to patient records and the retrospective nature of our study. Earlier achievement of full enteral nutrition in babies receiving probiotics

is biologically plausible with mechanisms similar to the protective effect against NEC[3-5]. Previous clinical evidence about a reduction in feed intolerance or the age at the achievement of full enteral nutrition in preterm infants remains variable. Small, prospective randomized control trials have reported a lower incidence of feed intolerance[12-14] and shorter time to regain birth weight and achieve full enteral nutrition in the study infants receiving probiotics[12]. On the other hand, other randomized trials have shown no difference in the time to attain full feeds between study and control infants[7,15] or of the volume of enteral feeds tolerated at 28 days after enrolment in the study[16]. Another randomized placebo-controlled trial has shown a decrease in "time to reach full feeds" in only infants with birth weight >1000 grams but not <1000 grams[17].

PICC line removal may also be dependent on other factors apart from the use of probiotics such as infant's overall clinical state, the difficulty of intravenous access and to some degree, on clinician preference and other known or unknown clinical practices. In this context, our nutrition guidelines and threshold for PICC line removal have remained unchanged over the study period. The majority of the PICC lines in both NPG and PG were removed only when not required, which further supports the validity of this study. One policy change over the review period has been a greater emphasis on antimicrobial stewardship, with a reduction in antibiotic exposure in the first week of life.

Our study excludes infants who never had a PICC line inserted but received IVN through an umbilical line. We note that there is no difference between the two groups in the age of insertion of the PICC lines and because all infants still requiring IVN beyond one week of age would have had a PICC line inserted (and the umbilical venous catheter removed), this is unlikely to have influenced the study results. It is also noteworthy that although we do use umbilical lines for IVN, we are more likely to use PICC lines in more immature babies who are likely to need IVN for a longer duration as highlighted by the median age of insertion of PICC line in our study. Another advantage of PICC lines in this group is the ability to place babies on Continuous Positive Airway Pressure support in the prone position.

In this retrospective, "before-after" cohort study we have been able to demonstrate earlier removal of PICC line in extremely preterm infants. Although some extraneous factors could have affected the results including its retrospective, non-randomized design, this is a clinically significant effect regarding reduction in adverse risks from PICC lines and IVN.

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