Journal of Neonatal Surgery 2018; 7:3
Doi: 10.21699/jns.v7i1.658

OPEN ACCESS

ORIGINAL ARTICLE

Safety of Probiotic Supplementation in Preterm Infants with Gastrointestinal Surgical Conditions: A Retrospective Audit

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How to cite: Abdul Hakeem M, Patole S, Keil A, Rao S. Safety of probiotic supplementation in preterm infants with gastrointestinal surgical conditions: a retrospective audit. J Neonatal Surg. 2018; 7:3.

ABSTRACT

Background: Limited data exists on the safety of probiotic supplementation in preterm infants with gastrointestinal (GI) surgical conditions.

Aims: To assess the safety of Bifidobacterium breve (B. breve) M-16V supplementation in preterm infants with GI surgical conditions in our unit with regards to probiotic sepsis.

Methods: This retrospective audit of prospectively collected data involved screening of neonatal databases to identify preterm infants (<33 weeks), who underwent surgery for GI conditions and received probiotics (January 2013 to October 2016). Probiotic sepsis was defined as the identification of Bifidobacteria in blood or other body fluids.

Results: Data on 33 preterm infants who underwent 43 GI surgeries and received probiotics was analysed. The median (IQR) gestation at birth and postnatal age at surgery was 30 (26.8-30.7) weeks, and 5 (1-34) days respectively. Twelve (36.3%) infants received probiotics in the preoperative period, 24 (72.7%) received it in the post-operative period, and 10 (30.3%) received it both in the pre-operative and post-operative period. The median (IQR) post-operative age at commencement, duration and number of doses of probiotics was day 10 (6-13), 43 (34-56) days, and 70 (61-100) respectively. Only one infant died; the reason for death was midgut volvulus. None developed Bifidobacterial sepsis.

Conclusions: Probiotic sepsis did not occur following B. breve M-16V supplementation in our small cohort of preterm infants with GI surgical conditions. Adequately powered randomised controlled trials are needed to confirm safety and efficacy of B. breve M-16V in this cohort.

Key words: Probiotics; Preterm infant; Gastrointestinal tract; Surgery; Sepsis.

INTRODUCTION

Systematic reviews of randomised controlled trials (RCT) have shown that probiotic supplementation improves the outcomes of preterm (non-surgical) infants [1-6]. The role of probiotics in neonates with gastrointestinal surgical conditions has not been explored adequately. Since these infants are exposed to multiple courses of antibiotics, receive enteral feeds slowly, and have less opportunities for skin to skin contact with their mothers, they are susceptible to develop gut dysbiosis through similar mechanisms that are operational in preterm infants [7-12]. Considering their beneficial properties, probiotics may improve the outcomes of neonates with surgical conditions of the gut.

However, since the gut integrity is disrupted by the disease process or the surgical procedure, neonates with gastrointestinal anomalies are theoretically at increased risk of developing sepsis due to the administered probiotic organism. There is limited data on the use of probiotics in neonates with gastrointestinal surgical conditions [17-19]. In our neonatal

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Submitted: 28-08-2017 Accepted: 22-11-2017
Conflict of interest: None Source of Support: Nil

intensive care unit (NICU), it is routine practice to give probiotic Bifidobacterium breve (B. breve)M-16V supplementation to all preterm infants born <33weeks' gestation (both surgical and non-surgical), which is continued till the postmenstrual age of 37weeks. Given the potential risks associated, we conducted this audit to assess the safety of probiotics in neonates with GI surgical conditions.

Aim of the study

To assess the safety of B. breve M-16V supplementation in preterm infants with GI surgical conditions in our unit.

MATERIALS AND METHODS

Type of study: A retrospective audit using prospectively collected data

Ethics Approval: The study was approved by the hospital's quality improvement committee as having met the 'Australian National Health and Medical Research Council requirements for quality assurance and audit projects'.

Participants: All preterm infants born <33 weeks gestation, who had gastrointestinal conditions requiring surgery and received probiotic supplementation either before and/or after surgery were included. This study was conducted at our Level 3 surgical neonatal intensive care unit (January 2013 to October 2016). Neonatal databases were screened to identify eligible infants. The data were collected from the medical records and discharge summaries of infants using a structured form. The idea behind our audit was to collect all the cases where in either gut mucosal integrity was interfered with or gut was manually handled during surgery. Probiotic associated sepsis was defined as the identification of Bifidobacteria in the blood or other body fluids in supplemented infants using DNA technology and routine culture techniques.

Probiotic (B. breve M-16V) protocol: The supplementation was started as single dose of 1.5 billion colony forming units (CFU) per day while on minimal enteral feeds and increased to two doses (3 billion CFU) per day when on full enteral feeds. The supplementation was withheld if the infant was not on feeds for any reason (e.g. sepsis, surgery, severe feed intolerance, critical illness).

Statistical Analysis: Statistical analysis was performed using Stata 13.0 (STATA Corp., TX, USA). The median, interquartile range (IQR), and range were calculated for data with skewed distribution. Percentages were calculated for categorical data. Given the small sample size and heterogeneity, analysis to compare the outcomes of infants who received probiotics in the pre-surgical period versus those who did not receive the supplements in the pre-surgical period was not done.

RESULTS

Thirty-three preterm infants who underwent 43 gastrointestinal surgeries and received probiotic were eligible for inclusion. Twenty-three (69.6%) infants underwent one episode of surgery whereas the remaining 10 (30.4%) had 2 episodes of surgery during their stay. Out of the 33 infants, 14(42.4%) were female. Indications for surgery included NEC (n=8), malrotation (n=5), non-NEC intestinal perforations (n=4), duodenal atresia (n=3), intestinal obstruction (n=3), tracheo esophageal fistula (n=3), pyloric stenosis (n=2), gastroschisis (n=2), esophageal perforation (n=1), hepatic cyst (n=1) and congenital diaphragmatic hernia (n=1). The median gestational age at the time of initial surgery was 30.8 weeks. The detailed demographic, anthropometry and feeding patterns have been described in table 1.

Of the 33 infants, 12 (36.3%) received probiotics before the surgery, 24 (72.7%) received after the surgery and 10 (30.3%) received both before and after surgery. The median post-operative day at the time of commencement of probiotics was day 10. The details of commencement of probiotic supplementation, relation to timing of surgical procedure, total number of dosages and total number of days of supplementation have been described in table 2.

All except one infant survived and were discharged home or transferred to regional hospitals. The infant who died had midgut volvulus with extensive necrosis. None of the supplemented infants developed sepsis due to the administered probiotic strain. One infant grew B. breve in the pleural fluid even before probiotics were commenced, due to cross colonization. Summary of all cases is described in table 3. Seven infants had blood stream infection due to Coagulase negative staphylococci (CONS), one had E Coli sepsis, one had CONS and Enterococcal sepsis, one had sepsis due to CONS and E Coli and one had sepsis due to CONS, E. coli and Enterobacter fecalis in the immediate peri operative period while they had not yet been commenced on probiotics supplementation. All of them responded to standard antibiotic regimens.

Table1. Demographic, anthropometry and feeding patterns of study infants

Characteristics	Median	Inter Quartile range	Range
Gestational age at birth (week)	30	26.8-30.7	23.1-32.3
Birth Weight (gm)	1058	900-1520	594-2460
Birth Weight Z score	0	-0.46 to +0.42	-1.86 to +2.45
Birth length (cm)	38	34-40	29-46
Birth length Z score	0	-0.79 to +0.59	-3.34 to +1.7
Birth head circumference (cm)	27	25-28	19.5-30.5
Birth head circumference Z score	0.7	-1.4 to +1.1	-3.29 to +1.42
Post-natal age at diagnosis (days)	4	1-32	1-47
Post-natal age at surgery (days)	5	1-34	1-48
Day of commencement of feeds in the post-operative period (day)	5.5	3-7	1-37
Postmenstrual age at commencement of feeds post op (week)	31.4	29.4-32.7	26.7-39.3
Post op day when full feeds achieved	18	11-21	1-78
Postmenstrual age at full feeds post op (week)	33.7	22-32.8	28.4-40.4
Number of days on antibiotics	24	9-41	3-108
Discharge Weight (gm)	2820	2350-3145	1840-5540
Discharge Weight Z score	0	-3.0 to -0.94	-5.09 to +1.04
Discharge length (cm)	47	46-49	38-61
Discharge length Z score	-1.34	-2.5 to -0.94	-6.26 to 0.9
Discharge head circumference (cm)	33.5	32-35.5	28-39
Discharge head circumference Z score	0.93	-1.6 to -0.34	-4.88 to 1.22
Duration of hospital stay (days)	76	55-110	21-159

Table 2: Details of probiotic supplementation

Characteristics	Median	Inter Quartile range	Range
Postmenstrual age at commencement of probiotics (weeks)	31.3	29.4-32.6	24.8-35
Postnatal age at commencement of probiotics (days)	9	6-14	2-58
Number of days prior to surgery when probiotics were commenced (N=13)	21	5-28	1-41
Duration of probiotic supplements in the pre-operative period (days) (N=13)	9	5-15	1-35
Post-operative day when probiotics were introduced (N=31)	10	6-13	2-30
Duration of probiotics in the post-operative period (days) (N=31)	45	29-52	3-122
Total duration of probiotics (pre-operative plus post- operative (days) (N=33)	43	34-56	9-128
Total doses of probiotics during hospital stay (pre- operative plus post- operative (days) (N=33)	70	61-100	9-210

DISCUSSION

This retrospective study of 33 preterm infants (<33 weeks' gestation) with GI surgical conditions describes our experience with the use of probiotic B. breve M-16V. Majority of the cases involved interference with gut mucosal integrity during surgery or by disease process e.g., NEC, non-NEC intestinal perforations, duodenal atresia, intestinal obstruction, tracheo esophageal fistula and esophageal perforation. Other cases involved manual handling of the gut during surgery which may result in altered physiological function and permeability e.g., malrotation, pyloric stenosis, gastroschisis, hepatic cyst and congenital diaphragmatic hernia. It was reassuring to know that none of our study infants developed peritonitis or blood stream infection due to the probiotic organism. It is also reassuring to know that none of the infants developed health care associated blood stream infections after commencement of the probiotic supplementation in post-operative period. All blood stream infections which occurred in the immediate perioperative period were when the probiotic supplementation had not yet been commenced. Analysis of difference between the groups was not attempted due to heterogeneity of cases and small sample size.

Standard laboratory techniques may not detect the probiotic organisms and hence may lead to false reassurance regarding the probiotic safety [20]. However, our microbiology laboratory is well equipped to detect B. breve in routinely collected specimens such as blood and other body fluids. This was demonstrated by the detection of B. breve species from the pleural fluid that was sent for routine microscopy and cultures on one of the study infants.

To our knowledge our study has the highest sample size so far on probiotic supplementation in preterm infants with GI surgical conditions. Our results add important data to the field of probiotic supplementation in this cohort. There are few studies reporting on tolerance of probiotic supplements in gastrointestinal surgical conditions in infants born >34 weeks. Powell et al. in their pilot randomized placebo-controlled trial found that administration of B. infantis American type, in 10 infants with gastroschisis born at >34 weeks gestation, was tolerated well and lead to good colonization of gut [18]. Murakami et al studied four term infants who required gut surgery and tolerated the supplementation of Bifidobacterium animalis subsp. Lactis [19].

There are few case reports of probiotic sepsis in neonates undergoing gut surgery. Brecht et al. reported a case of Lactobacillus sepsis 52 days following a second laparotomy for spontaneous intestinal perforation in a preterm infant. The infant had received Infloran (a combination of B. bifidum and Lactobacillus acidophilus) from 7 days after the second laparotomy [13].

Table 3.Description of Individual cases

Serial No	Preoperative condition/ Diagnosis	Duration of Probiotic (days)		Day of life at initial Surgery	Outcome
		Pre-op	Post-op		
1	NEC	0	69	3	Survived & No probiotic sepsis
2	Malrotation	0	35	3	Survived & No probiotic sepsis
3	Malrotation	0	11	4	Survived & No probiotic sepsis
4	Malrotation	0	51	7	Survived & No probiotic sepsis
5	Malrotation	0	45	2	Survived & No probiotic sepsis
6	Duodenal atresia	0	49	3	Survived & No probiotic sepsis
7	NEC	9	0	27	Survived & No probiotic sepsis
8	CDH	0	53	5	Survived & No probiotic sepsis
9	TOF	0	34	1	Survived & No probiotic sepsis
10	NEC	0	35	28	Survived & No probiotic sepsis
11	Spontaneous intestinal perforation	0	65	1	Survived & No probiotic sepsis
12	Pyloric stenosis	42	0	48	Survived & No probiotic sepsis
13	TOF	0	56	2	Survived & No probiotic sepsis
14	Esophageal perforation, pleural effusion, pneumothorax	0	71	5	Pleural fluid grew Bifidobacterium due to cross colonization
15	NEC	14	7	32	Survived & No probiotic sepsis
16	NEC	8	13	34	Survived & No probiotic sepsis
17	Intestinal obstruction, meconium ileus	2	89	22	Survived & No probiotic sepsis
18	Gastroschisis, ileal atresia	0	36	5	Survived & No probiotic sepsis
19	Spontaneous Ileal perforation	3	48	13	Survived & No probiotic sepsis
20	Pyloric stenosis	28	3	35	Survived & No probiotic sepsis
21	Ileal atresia	9	46	31	Survived & No probiotic sepsis
22	Duodenal atresia	0	15	1	Survived & No probiotic sepsis
23	TOF	0	36	1	Survived & No probiotic sepsis
24	NEC	0	29	5	Died due to midgut volvulus with extensive necrosis, No probiotic sepsis
25	Internal hernia	15	28	44	Survived & No probiotic sepsis
26	NEC	20	75	25	Survived & No probiotic sepsis
27	Spontaneous ileal perforation	0	37	2	Survived & No probiotic sepsis
28	Malrotation	5	62	10	Survived & No probiotic sepsis
29	NEC	0	42	4	Survived & No probiotic sepsis
30	NEC	6	122	10	Survived & No probiotic sepsis
31	Gastroschisis, bowel atresia	0	94	2	Survived & No probiotic sepsis
32	Hepatic cyst	0	49	1	Survived & No probiotic sepsis
33	Duodenal atresia	0	26	5	Survived & No probiotic sepsis

Kunz et al. described 2 cases of probiotic sepsis. One was a male infant born at 36 weeks gestation and underwent gut resection for congenital intestinal atresia and volvulus. Lactobacillus GG supplementation was commenced on 95th day of life. On 23rd day of supplementation, he developed sepsis and showed growth of Lactobacillus in the blood culture. Other infant was a 34-week gestation male with gastroschisis who underwent gastrostomy and jejunostomy shortly after birth and commenced on Lactobacillus GG on day 17 of life. He developed Lactobacillus sepsis on day 186 of life [14]. Ohishi et al. reported an infant with omphalocele for which surgery was performed on the day of birth and Bifidobacterium breve BBG-01 supplementation was commenced on day 2 of life. The infant developed sepsis with the genetically same Bifidobacterium on day 12 of life [15]. Zbinden et al. reported a 29 week female infant who was commenced on Infloran (combination of Bifidobacterium longum and Lactobacillus acidophilus) on the day of birth and developed NEC on day 11 of life that required laparotomy. At the same time blood cultures grew B. longum [16].

The limitations of our study include the retrospective design without controls, heterogeneous nature of the surgical conditions and the small sample size. Another limitation was the fact that we did not do routine fecal microbiota studies to assess gut dysbiosis. While the results of our study are reassuring, the reports of probiotic sepsis in surgical neonates described above, suggest the need for caution and the need for well conducted RCTs in this high-risk population. Such RCTs should be adequately powered to evaluate clinically relevant outcomes such as mortality, healthcare associated blood stream infections (HABSI), ventilator associated pneumonia, other hospital acquired infections (HAI), duration of antibiotic therapy, gut microbiota, inflammatory markers (e.g., high sensitivity C-Reactive Protein), feed tolerance, scores of physical growth at the time of discharge and most importantly, sepsis due to the supplemented probiotic organism. Stratification of the study participants based on the underlying surgical condition would also be essential, given the heterogeneous nature of the gastrointestinal surgical conditions in neonates.

CONCLUSION

Probiotic sepsis did not occur following B. breve M-16V supplementation in our small cohort of preterm infants with gastrointestinal surgical conditions. Adequately powered randomised controlled trials are needed to confirm the safety and efficacy of B. breve M-16V in this cohort. Note: Following this audit, we are in the process of conducting a RCT in near future.

Authors' contribution: All authors equally contributed in concept, design, manuscript writing, and approved final version.

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