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**Effectiveness of two probiotics in the prevention of necrotizing enterocolitis in a cohort of very-low-birth-weight premature newborns**

Jose Uberos – MD, PhD; *Neonatal Intensive Care Unit. San Cecilio Clinical Hospital. Avda. Dr. Oloriz 16, 18012 Granada (Spain). Medicine Faculty. Granada. Avda. de la Investigación 11; 18016 Granada (Spain). FAX +34 958 246661.* [*juberos@ugr.es*](mailto:juberos@ugr.es)

Ana Campos-Martinez - PhD; *Neonatal Intensive Care Unit. San Cecilio Clinical Hospital. Avda. Dr. Oloriz 16, 18012 Granada (Spain). FAX +34 958 246661.* [*anacamposmar@gmail.com*](mailto:anacamposmar@gmail.com)

Elizabeth Fernandez-Marín - PhD; *Neonatal Intensive Care Unit. San Cecilio Clinical Hospital. Avda. Dr. Oloriz 16, 18012 Granada (Spain). FAX +34 958 246661.* [*elifermarin@hotmail.com*](mailto:elifermarin@hotmail.com)

Enrique Blanca-Jover - MD, PhD; *Neonatal Intensive Care Unit. San Cecilio Clinical Hospital. Avda. Dr. Oloriz 16, 18012 Granada (Spain). FAX +34 958 246661.* [*enriblanca@hotmail.com*](mailto:enriblanca@hotmail.com)

Isabel Cubero Millan - PhD; *Neonatal Intensive Care Unit. San Cecilio Clinical Hospital. Avda. Dr. Oloriz 16, 18012 Granada (Spain). FAX +34 958 246661.* [*isacubero83@hotmail.com*](mailto:isacubero83@hotmail.com)

Aida Luiz Lopez - PhD; *Neonatal Intensive Care Unit. San Cecilio Clinical Hospital. Avda. Dr. Oloriz 16, 18012 Granada (Spain). FAX +34 958 246661.* [*aida.ruiz@hotmail.com*](mailto:aida.ruiz@hotmail.com)

**Running title:** Probiotics in very-low-birth-weight newborns

**ABSTRACT**

Some studies have reported a decreased incidence of enterocolitis necrotizing after supplementation with probiotics. However, few studies have considered the equivalence or otherwise of different strains in preventing enterocolitis necrotizing in newborns. A prospective observational study was conducted in a cohort of 291 VLBW newborns, designed to assess the prevalence of enterocolitis necrotizing after receiving supplementation with the probiotic Inforan® (Berna Biotech, Madrid, Spain) 250 mg capsules containing 109 colony forming units (CFU) *Lactobacillus acidophilus* (ATCC 4356) and 109 CFU *Lactobacillus. bifidum* (ATCC 15696) (European Medicines Agency, 2014); Bivos® (Ferring, Madrid, Spain) containing Lacticaseibacillus rhamnosus (LGG) (ATCC 53103) (109 CFU); or no probiotic. Statistical analysis was performed using multivariant regression with days of parenteral nutrition, NICU stay, oxygenotherapy and chorioamnionitis. 173 VLBW newborns received probiotic supplementation, 65 received Infloran® and 108 Bivos®. In 72 VLBW newborns no probiotic was administered. We observed a significant association between reduction of necrotizing enterocolitis ≥ grade 2 and probiotic use. For Infloran® OR 0.174 (CI 95% 0.032, 0.936), for Bivos® OR 0.196 (CI95% 0.053, 0.732). Although both probiotics are associated with a lower prevalence of necrotizing enterocolitis in VLBW newborns, the comparison between Infloran® or Bivos® does not show significant differences.

**KeyWords.** Infant, Premature; Probiotics; Necrotizing enterocholitis; Morbidity

**INTRODUCTION**

Necrotising enterocolitis (NEC) is the gastrointestinal pathology that most frequently affects very-low-birth-weight (VLBW) infants, the risk increases with younger gestational age. NEC has significant repercussions on VLBW newborns, including neurodevelopmental disorders and increased mortality.

Among other explanations suggested, the pathogenesis of NEC has been ascribed to an excessive inflammatory response and immature innate immunity. However, according to epidemiological studies, the risk is reduced by preferential feeding of breast milk and the development by neonatal units of standardised nutrition protocols (Hwang et al., 2013).

The bacteria generally used as probiotics are lactobacilli and bifidobacteria. After passing through the stomach and small intestine, some probiotics survive and colonize the large intestine (Gewolb et al., 1999; Jacobi et al., 2012) . This differential finding has been addressed in many trials conducted to consider supplementation schemes with probiotics for VLBW newborns. In the intestinal mucosa, the body’s defences have two main components: on the one hand, the host’s immune response, and on the other, the barrier function exerted by the intestinal microbiota, through a mechanism of competitive inhibition within the ecological niche. In special situations, such as that of VLBW infants admitted to intensive care units, low levels of colonisation by bifidobacterium and lactobacillus can be observed, and the intestinal microbiota are modified, with an increased presence of proteobacteria, represented by *Klebsiela*, *Enterobacter*, *Citrobacter* and *Pseudomonas*, all of which are common within the hospital environment and are responsible for the development of late sepsis and NEC in VLBW infants.

With respect to probiotics, the effect of a bacterium is known to be specific to the strain to which it belongs and cannot be extrapolated to other strains of the same species; therefore, each strain has unique properties, with different physiological functions. The assignment of a beneficial effect to a particular strain depends on the conditions of use, the population group to which it is directed and, very particularly, on the dose supplied (Murguia-Peniche et al., 2013) .

After the use of probiotics, it is important to avoid bacterial metabolic activity that might be harmful to the host, associated with the risk of excessive deconjugation or hydroxylation of bile salts in the small intestine, high levels of hydrolase activity on bile salts (deconjugation) and excessive degradation of the mucin layer of the intestine, any of which could favour intestinal colonisation by potentially pathogenic strains (Oh, 2018).

Studies have shown that some strains of probiotics may be useful in the prophylaxis of NEC in VLBW newborns (Alfaleh et al., 2014; Uberos et al.,2017). However, very little research has been undertaken to determine the clinical equivalence of the different formulations used in neonatology. In the present study, our aim is to establish whether the effectiveness of the probiotics *L. bifidum* + *L. acidophilus* (Infloran®) or *L. rhamnossus* (LGG) (Bivos®), which are commonly used in our neonatal unit for the prevention of NEC in VLBW newborns.

**METHOD**

In this prospective observational study we compare the effectiveness and equivalence of two probiotics commonly used for the prevention of NEC in VLBW newborns. In our neonatal intensive care unit (NICU), supplementation with probiotics was started in December 2013 for VLBW newborns and became part of standard practice, in accordance with guidelines in this respect published by the Nutrition and Neonatal Metabolism Group of the Spanish Society of Neonatology (Narbona, 2014). On the basis of these recommendations and after reviewing the evidence available, the hospital Pharmacy Committee proposed the use of two commercial formulations. The parents/guardians of the participants are asked for authorization. The study protocol was approved by the hospital’s Ethics Committee (Verification code: b1072175150294535cb06bd44a5ca9ddfe619d24), and all current regulations regarding data confidentiality were respected.

***Morbidities*** For the diagnosis of NEC, patients were classified according to the Bell criteria (Bell, 1978). The presence of any grade of bronchopulmonary dysplasia (BPD) was also recorded. According to the NIHCD definition (Ehrenkranz et al. 2005) and to Jobe and Bancalari (Jobe and Bancalari, 2001), BPD is present when the oxygen requirement is >21% at 28 days of life and/or when the oxygen requirement is >21% or there is positive airway pressure at 36 weeks’ corrected gesta­tional age. The level of BPD is classed as mild, moderate or severe. Clinical sepsis was diagnosed when a score ≥ 8 on the NOSEP-1 scale was obtained. This score was determined as follows: PCR ≥ 1.4 mg/dl (5 points), neutrophils >50% (3 points), thrombocytopaenia <150 x 109/L (5 points), fever >38.2ºC (5 points) and total parenteral nutrition ≥ 14 days (6 points) (Mahieu et al., 2000). The diagnosis and staging of retinopathy of prematurity (ROP) are based on retinal examination before discharge. Severe ROP was defined as stages 3-5 (International Committee for the Classification of Retinopathy of Prematurity, 2005). In ROP, the presence of at least one of the follow­ing findings meant the eye was classified as having an unfavourable outcome: a retinal fold involving the macula; a retinal detachment in­volving zone I of the posterior pole; retrolental tissue, or “mass” (Lad et al., 2009). The diagnosis of intraventricular haemorrhage (IVH) was based on the Papile grading system (Papile et al., 1978). In all newborns, a trans­fontanellar ultrasound was performed on the third day of life and then every week. Persistent ductus arteriosus (PDA) was diagnosed by Doppler ultrasound and treated when clinical repercussions were observed or when the diameter was greater than 2 mm. Cholestasis was defined as an increase in direct bilirubin values > 2 mg/dL (34.2 μmol/L).

***Nutritional management.*** Enteral and parenteral nutrition were conducted following the recommendations of the Nutrition and Metabolism Group of the Spanish Neonatology Society (Narbona et al., 2014) and the standard protocol of our NICU. Accordingly, all clinically stable newborns were given minimal enteral nutrition with breast milk (or formula for preterm infants) at a rate of 1 ml/kg every three hours, from the first day of life, with subsequent increases in enteral nutrition, according to tolerance, at a rate of 15-25 ml/kg/day, until full enteral nutrition was achieved. The fortification of breast milk was considered after volumes >80 ml/kg/day were reached.

***Protocol for the administration of probiotics.*** Since December 2013, our NICU has used two presentations of probiotics, Infloran® (Berna Biotech, Madrid, Spain) 250 mg capsules containing 109 colony forming units (CFU) *L. acidophilus* (ATCC 4356) and 109 CFU *L. bifidum* (ATCC 15696) (European Medicines Agency, 2014). A daily dose of one capsule every 12 hours was dissolved in 2 ml of (breast or formula) milk and supplied via nasogastric tube; Bivos® (Ferring, Madrid, Spain) containing *L. rhamnnosus* (LGG) (ATCC 53103) (109 CFU). A daily dose of 9 drops every 24 hours was dissolved in 2 ml of (breast or formula) milk and supplied via nasogastric tube; the probiotic supplementation was started at the first enteral feed of at least 1 ml per bolus and was continued until 35 weeks postmenstrual age or until discharge from the NICU. The choice of the type of probiotic or no probiotic was left to the free choice of the Neonatologist who assists the newborn.

***Statistical considerations.*** The descriptive data were summarised using medians and interquartile intervals for the continuous variables and distribution frequencies for the categorical variables. The univariate comparisons for the continuous variables were made by the Mann-Whitney test and for the categorical variables by the chi-square test. The association of comorbidities in VLBW newborns and supplementation with one type or another of probiotic was evaluated with a multinomial regression analysis, adjusting for days of central catheter, parenteral nutrition, oxygenotherapy and breastfeeding. The analysis was performed using IBM SPSS 20.0 for Windows software (IBM, Armonk, NY).

**RESULTS**

A total of 245 newborns weighing <1500 g were treated with probiotic, from December 2013 to November 2020, with one of the probiotics analysed in this study or no probiotic; 65 received Infloran®, 108 Bivos® and 72 no received probiotic (Figure 1).

Table 1 shows the characterisitics of the maternal and neonatal variables in the group supplemented with Infloran®, Bivos® or no supplementation. We observed significantly more cases of chorioamnionitis in the group without any supplementation. In relation to neonatal variables, we observed a longer duration of stay in the NICU among newborns who received probiotic supplementation, with a longer duration of parenteral nutrition. No adverse effects were recorded after the use of probiotics.

We also observed a shorter duration of oxygen therapy in newborns who did no receive probiotic supplementation. These variables that showed deviations in the different groups were used as adjustment variables in models of regression (Table 3).

Table 2 shows the incidence of comorbidities in each group, we significantly observed a higher prevalence of NEC ≥2 in newborns who did not receive probiotic supplementation. We observed a significant association between probiotic supplementation and NEC ≥2, for Infloran® OR 0.174; p<0.05 (CI 95% 0.032, 0.936) and OR 0.196; p<0.01 (CI 95% 0.053, 0.732) for Bivos®. We did not observe associations with statistical significance for comorbidities studied (Table 3). We did not observe significant differences in the prevalence of NEC ≥2 between those newborns who received Infloran® or Bivos®.

**DISCUSSION**

The results obtained show that routine supplementation with a combination of *L. acidophillus* + *L. bifidum* (Infloran®) or *L. rhamnnosus* (LGG) (Bivos®) are effective in preventing NEC in the VLBW newborns.

According to previous research, the use of probiotics reduces mortality, and the outcomes obtained do not vary according to the type of probiotic used (Bernardo et al., 2013; Uberos et al., 2017). In our cohort, we observed more cases of NEC ≥2 in VLBW newborns without probiotic supplementation despite the fact that the birth weight in this group is slightly higher.

Although meta-analyses of experimental and observational studies have confirmed the benefits of routine probiotic supplementation in the prevention of NEC for VLBW newborns, Kane et al. (Kane et al., 2018) studied 175 VLBW newborns who received supplementation with LGG, and reported an increase in NEC compared to the period prior to routine supplementation. However, these authors did not include in their analysis the incidence of late sepsis or the duration of central venous catheter use before and after the start of routine supplementation, and these aspects might account for the differences observed in the incidence of NEC. Furthermore, the same authors reported a higher rate of BPD and a greater need of inotropic drugs among the patients supplemented with LGG. These variables, too, may be related to the incidence of NEC. In another observational study, Meyer and Alexander (Meyer et al., 2017) measured a reduced risk of NEC after supplementation in VLBW newborns with LGG and lactoferrin. The components of the intestinal microbiota, such as *L. acidophillus* with *B. bifidum*, have been used for decades in the treatment of gastrointestinal disorders. Samuels et al. (Samuels et al., 2016) in a quasi-experimental study, observed no significant changes in the odds ratio (OR) for NEC in patients supplemented with *L. acidophillus* and *B. bifidum*. Multicenter observational studies on a sample of 25,821 newborns show that after supplementation with probiotics, severe forms of NEC and mortality decrease, although the overall incidence of NEC remains stable 8.8% (Zocaya et al., 2020).

The result of an intervention, in terms of decreased OR, depends on the incidence of the condition, and therefore in hospitals with a low incidence of NEC the expected effect of an intervention on the OR will obviously require a larger sample than that where the incidence is higher. Lin et al. (Lin et al., 2008) in an experimental study comparing placebo and the combination of *L. acidophilus* with *B. bifidum*, observed a reduction in mortality and in the incidence of NEC. Another systematic review, by Baucells et al. (Baucells et al., 2016) analysed the findings of nine experimental studies based on 3521 VLBW newborns and concluded that the combination of *L. acidophilus* with L*. bifidum* produced most benefit in the prevention of NEC and mortality. The latter findings are in line with our own observations (Table 2).

The main limitation of our study with a prospective observational design derives precisely from the absence of randomization, which implies a greater possibility of selection bias.

The main conclusion drawn from the present study is that the alternatives of nutritional supplementation in VLBW newborns with Infloran® or with Bivos® in the prevention of NEC they are effective, we did not observe differences in the prevalence of NEC after the use of Infloran® or Bivos®. We believe that our data may be of interest in conducting larger meta-analysis studies.

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**Author contribution.** All authors have read and approved the final manuscript. JU - designed the research study and drafted the manuscript. EBJ, ACM and EFM coordinated and prepared the database and analysed the data.

**Compliance with ethical standards**

**Conflict of interest statement.** The authors have no relevant conflicts of interest to declare.

***Ethical considerations.*** The protocol was approved by the Ethics Committee of the Hospital and all current regulations regarding data confidentiality were complied with.

**Data Availability Statement.** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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***Figure 1.*** *Flow diagram for the VLBW newborns included in the study (From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097).*

**Table 1**. Characteristics of the maternal and neonatal variables

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **Infloran****®,**  **n=65** | **Bivos®,**  **n=108** | **No Probiotic,**  **n=72** | **p-value** |
| **Maternal** | n (%) | n (%) | n (%) |  |
| PIH | 10 (15.3) | 14 (12.9) | 21 (29.1) | 0.62 |
| Chorioamnionitis | 5 (7.7) | 15 (13.8) | 28 (38.8) | 0.01 |
| Antibiotics | 27 (41.5) | 51 (47.2) | 47 (65.2) | 0.61 |
| Glucocorticoids | 47 (72.3) | 84 (77.7) | 66 (91.6) | 0.21 |
| PPROM | 22 (33.8) | 31 (28.7) | 24 (33.3) | 0.09 |
| Gestation (w)\* | 30 (28, 31) | 29 (28, 31) | 30 (27, 32) | 0.21 |
| Gestation ≤ 27 w | 13 (20) | 25 (23.1) | 36 (50.0) | 0.24 |
| Twin birth | 29 (44.6) | 50 (46.3) | 44 (61.1) | 0.38 |
| Caesarean section | 53 (81.5) | 86 (79.6) | 63 (87.5) | 0.40 |
| **Neonatal** |  |  |  |  |
| Birth weight (g)\* | 1219 (999, 1426) | 1203 (915, 1431) | 1346 (1100, 1500) | 0.60 |
| Birth weight (z-score)\* | -0.64 (-1.26, 0.002) | -0.48 (-1.09, -0.02) | -0.57 (-1.40, 0.34) | 0.36 |
| Weight 7 days (z-score)\* | -1.29 (-1.70, -0.73) | -1.24 (-1.70, -0.66) | -1.18 (-1.67, -0.55) | 0.54 |
| Male gender | 35 (53.8) | 60 (55.5) | 45 (62.5) | 0.92 |
| Apgar ≤7 (5 min) | 24 (36.9) | 38 (35.1) | 20 (27.7) | 0.15 |
| SGA | 16 (24.6) | 26 (24.1) | 20 (27.7) | 0.96 |
| Breast milk | 44 (67.6) | 68 (62.9) | 57 (79.1) | 0.82 |
| Length of NICU stay (d)\* | 29 (18-39) | 29 (19-44) | 20.5 (10.7, 32.7) | 0.01 |
| Central venous catheter (d)\* | 9.5 (4, 17) | 9.5 (4, 17) | 7 (3, 17) | 0.29 |
| Age at full feeds (d)\* | 10 (7, 16.7) | 11 (8, 19.7) | 10 (6, 15.5) | 0.15 |
| Parenteral nutrition (d)\* | 11.5 (7, 21) | 11 (7, 19.5) | 8 (4, 16) | 0.02 |
| **Respiratory support** |  |  |  |  |
| Oxygen \* | 19 (6, 42.5) | 26.5 (6.7, 48.2) | 10 (3, 33) | 0.03 |
| CPAP \* | 3 (2, 5.7) | 3 (1, 7.2) | 2 (1, 4.5) | 0.05 |
| Mechanical ventilation \* | 1 (0, 3.5) | 1 (0, 6) | 0 (0, 3) | 0.33 |

\*Median (IQR). P-valor Χ2 for qualitative analysis, Mann Whitney for quantitative analysis.

T1 -Infloran® (Berna Biotech, Madrid, Spain). T2 - Bivos® (Ferring, Madrid, Spain). PIH: Pregnancy induced hypertension, PPROM: Preterm pre-labour rupture of membranes, SGA: Small gestational age, CPAP: Continuous positive airway pressure.

**Table 2.** Comorbidities for VLBW newborns with Infloran**®** or Bivos**®** supplementation.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Infloran®**  **(n=65)** | **Bivos®**  **(n=108)** | **No Probiotic,**  **n=72** | **p-value** |
|  | n (%) | n (%) | n (%) |  |
| BPD | 21 (32.3) | 45 (41.6) | 25 (34.7) | 0.13 |
| NEC ≥ Stage II | 5 (7.6) | 8 (7.4) | 14 (19.4) | 0.03 |
| Need for surgery | 0 (0) | 1 (0.9) | 4 (5.5) | 0.13 |
| Exitus after NEC | 0 (0) | 1(0.9) | 3 (4.1) | 0.17 |
| PDA | 11 (16.9) | 21 (19.4) | 13 (18.1) | 0.81 |
| IVH |  |  |  |  |
| Grade I-II | 6 (9.2) | 14 (12.9) | 14 (19.4) | 0.38 |
| Grade III-IV | 0 (0) | 3 (2.7) | 4 (5.5) | 0.15 |
| ROP | 4 (6.1) | 12 (11.1) | 4 (5.5) | 0.36 |
| Sepsis | 17 (26.1) | 24 (22.2) | 22 (30.5) | 0.85 |
| Cholestasis | 11 (16.9) | 15 (13.8) | 7 (9.7) | 0.23 |

\* Counts and percentages; T1 -Infloran® (Berna Biotech, Madrid, Spain). T2 - Bivos® (Ferring, Madrid, Spain). BPD: Bronchopulmonary dysplasia. PDA: Patent ductus arteriosus, IVH: Intraventricular haemorrhage, ROP: Retinopathy of prematurity.

**Table 3.** OR of the comorbidities of VLBW newborns supplemented with Infloran**®** or Bivos**®** .

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **OR (CI 95%)**  **Unadjusted** | | **OR (CI 95%)**  **Adjusted \*** | |
|  | **Infloran®** | **Bivos®** | **Infloran®** | **Bivos®** |
| NEC ≥ Stage II | 0.506  (0.174, 1.467) | 0460  (0.186, 1.137) | 0.174 ¶  (0.032, 0.936) | 0.196 ¶¶  (0.053, 0.732) |
| BPD | 1.250  (0.619, 2.523) | 1.830  (0.999, 3.351) | 0.942  (0.373, 2.379) | 1.900  (0.869, 4.153) |
| PDA | 1.390  (0.588, 3.284) | 1.568  (0.751, 3.276) | 0.931  (0.283, 3.066) | 1.436  (0.528, 3.907) |
| IVH |  |  |  |  |
| Grade I-II | 0.612  (0.226, 1.654) | 0.848  (0.392, 1.834) | 0.652  (0.216, 1.971) | 0.800  (0.322, 1.990) |
| Grade III-IV | - | 0.209  (0.058, 0.756) | - | 0.478  (0.073, 3.140) |
| ROP | 1.127  (0.288, 4.410) | 2.070  (0.695, 6.168) | 3.316  (0.428, 25.685) | 5.552  (1.002, 30.752) |
| Sepsis | 1.243  (0.598, 2.583) | 1.074  (0.566, 2.040) | 0.756  (0.314, 1.821) | 0.643  (0.294, 1.407) |
| Cholestasis | 2.420  (0.913, 6.413) | 1.755  (0.709, 4.343) | 2.943  (0.865, 10.005) | 1,418  (0.454, 4.430) |

\* Adjusted for days of parenteral nutrition, length of NICU stay (days) oxygenotherapy (days) and chorioamnionitis. ¶ = p<0.05, ¶¶ = p≤0.01.

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