



Probiotics use in a neonatal unit in Port Sudan / Sudan: This combination is effective and should be part of the routine care

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General Note

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ABSTRACT

Background: Survival of preterm neonates resulted in a multitude of morbidities. One of the efforts to decrease this is the use of probiotics. Worldwide many investigators tested a probiotic or another. In the effort to reduce neonatal mortality in Sudan, the author tried three combined probiotics. To my knowledge, worldwide nobody had tested such a combination, no such research in Sudan or in the Arabic World at the moment.

Objectives: The primary objective is to test effect on incidence of feeding intolerance, NEC, sepsis, and death in the study group, compared to the historical cohort of infants of same gestational age groups, not given probiotics. The secondary objective is to test drug tolerability, side effect, prevention of nosocomial infection, and length of hospitalization in the study group.

Method: This is a pilot unicentral, longitudinal prospective, hospital – based study, included preterm infants 26 to 37 wks of gestation. Exclusion criteria: severe congenital malformations, GIT defects, refusal of one/both parents. 250,000,000 mixed bacterial units is given orally, OD. Duration of treatment per infant was till maturity. Data analysed by SSPS 20 and manually.

Results and Conclusion: The intervention effectively decreased the mortality ($p < 0.03$) and morbidity ($p < 0.02$) and abolished feeding intolerance, is well tolerated, has no adverse effect, and significantly shorten the hospitalization period ($p < 0.05$).

Key words: combined Probiotics, preterm infants, mortality, NEC, sepsis, feeding intolerance, nosocomial infections.

1. INTRODUCTION

Depending on the mode of delivery, the sterile GIT of the foetus is being colonized with different organisms immediately after birth, (from maternal skin in C/S delivery, or birth canal in per vaginum delivery). Then invasion occurs due to bacterial translocation [1- 3], renders them prone to sepsis, necrotizing enterocolitis (NEC), and death beside other specific problems of this age, like feeding intolerance etc. It is recently suggested that probiotics can prevent diseases and improve short and long term health of sick preterm infants, though there is no consensus.

Probiotics are live microorganisms that modulate intestinal ecosystem (IES) and confer many health benefits. Their many putative effects like normalization of the intestinal microflora, reduction of the bacterial translocation and sepsis, are obtained via increasing mucosal barrier by occupying the binding sites and thence reducing the intestinal permeability. They also decrease the pro-inflammatory and increase the anti-inflammatory cytokines. Accordingly, these microbiota found to have beneficiary roles in many preterm infant's specific conditions like prevention of NEC, enhancement of the immunity and brain and intestinal development. Thence improving feed tolerance and reducing hyperbillirubinaemia in very low birth weight (VLBW) infants, and later, prevention of colics [2-6].

In Sudan, premature delivery is on rise due to multifactor. Survival of the preterm neonates resulted in a multitude of innate morbidities. Many harmful traditions and believes applied on the neonate, like cauterization of gum and skin, or giving water, glucose, dates etc, that change the normal flora to a pathological bacteria, lead to NEC or invade the blood and lead to sepsis and death. The neonatal mortality rate in Sudan is 33/1000 live birth, accounting for 39% of under five deaths according to Sudan National Newborn Health Strategy and Action Plan: 2016 – 2020. In the effort to reduce this high neonatal mortality (18% in our center alone) and morbidity in our city, the author tried the probiotics used in adult medicine (as there is no available special solution for neonate or children), composed of 3 probiotic bacteria: *L. Acidophilus*, *L. Casei* and *L. Rhamnosus*, concentrated to 2 billion bacterial units per capsule), in certain dose, for preterm infants admitted to the neonatal unit. Most reasearchers tested one or another type of probiotic bacterium on prevention of NEC or nosocomial infection, but to my knowledge, worldwide, nobody had tested a three combined probiotics like such, no such research in Sudan, no such trial in the Arabic World before initiation of this trial.

2. METHOD

This is a pilot unicentral, longitudinal prospective, hospital –based study. The approval for the study was taken from the ethical committee of the Sea Port Corporation hospital (SPCH), and a verbal consent was taken from both parents to use this drug in their admitted preterm infants with intension to prevent morbidity and to decrease mortality. Morbidity is defined as NEC, feeding intolerance, sepsis. All preterm infants 26 to 37 wks of gestation were included. Those with severe congenital malformations or GIT defects or refusal of one/both parents, were excluded. Probiotane capsule from Vitane company (the agent is Pharma Trading Company) contains *L. Acidophilus*, *L. Casei* and *L. Rhamnosus*, concentrated to 2 billion bacterial units (36mg). The content of one

capsule is dissolved in an 8 mL of distilled water or freshly expressed breast milk, to yield 250,000,000 (250 million) bacterial unit per mL, (= 4.5 mg/ mL of lactobacilli culture), then one mL is given per oral to the preterm, OD whenever the oral trophic feeds started. Duration of treatment per infant is till maturity or death.

3. RESULTS

From the total hospital delivery (5248) during the period of the study (1/1/2014 – 31/12/ 2016), 712 infant (13.6%) were admitted to nursery. Preterm delivery (≤ 37 wks) were 223 infants (31.3%). 49 infants (22%) were exprem less than 30 wks (10 were 26 - < 28 wks, 39 were 28 - < 30 wks), see figure 1.

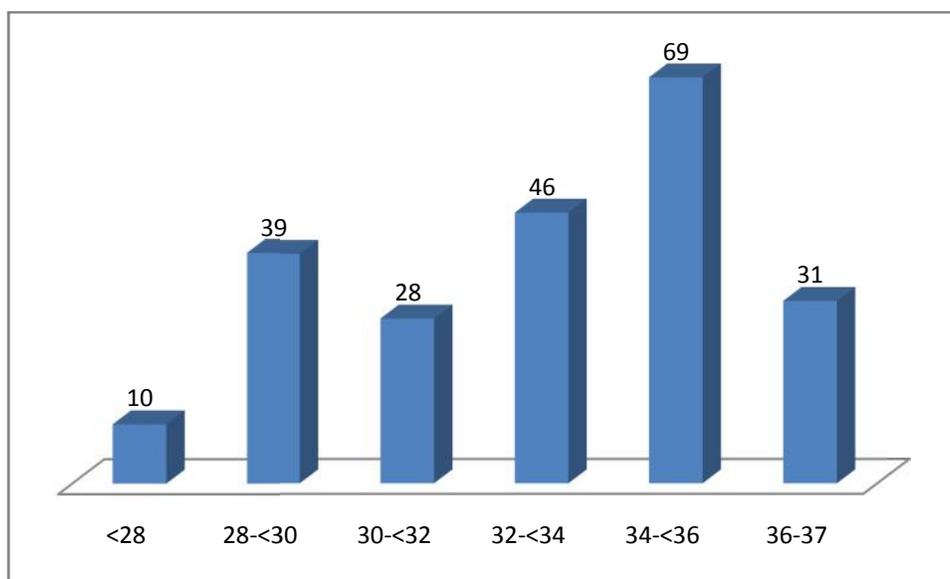


Figure 1 Distribution of infants according to gestational age

Necrotizing enterocolitis (NEC) and or sepsis occurred in 12 infants of the total nursery admission in the study group (5.4%), deaths were 12 (5.4%), only one infant (0.5%) was suspected to have drug/ feed intolerance in form of vomiting, but really could not definitely attributed to the drug or the feed, as we stopped both for 2 days and then resumed it without recurrence of vomiting (see table 1). The mean length of hospitalization across all gestational age groups was 13.4 days.

Table 1 The study group: morbidity, deaths, and discharges

Age (wks)	Morbidity		Death	Discharge	Total No
	Sepsis/NEC	intolerance			
26 - < 30	1	0	4	45	49
30 - < 32	4	0	3	25	28
32 - < 34	3	1	3	43	46
34 - < 36	4	0	2	67	69
36 - \leq 37	0	0	0	31	31
Total	12	1	12	211	223

The historical control group

Total delivery in the period 1/1/2011 to 31/12/2012 were 2690. Total number admitted to nursery was 304, (11.3%), preterm infants less than 37 wks were 76 (25%).

Sepsis and NEC cases among preterm infants were 40 (52.6%), deaths were 16 (21%). The difference is statistically significant when comparing the number of sepsis and NEC in the historical control group (52.6%) to that in study group (5.4%), $p < 0.02$, and

same for number of deaths (21% to 5.4% respectively, $p < 0.03$). in this historical control group, the mean hospitalization time across all gestational age groups of preterm infants was 27.2 days.

Table 2 Comparison between the control and study cohorts

Variable	Control group	Study group	p- value
NEC/ sepsis	40 (52.6%)	12 (5.4%)	< 0.02
Death	16 (21%)	12 (5.4%)	< 0.03
Time to discharge (mean)	27.2 days	13.4 days	< 0.05

4. DISCUSSION

The survival of preterm infants as a result of advanced neonatal care has resulted in many morbidities that can lead to death or prolonged hospitalization with its all burdens. Accordingly, this field is being under continuous research and innovations. One of the latest is the use of probiotics in neonatal care. Many researchers investigated different types of probiotics, most are single bacterium [7 - 11], with different results. A single study (the ProPrems Trials) tested a different combination of 3 probiotics, namely: Bifidobacterium infantis, Streptococcus thermophilus and Bifidobacterium lactis on late onset sepsis in premature infants less than 32 wks, with also, promising results [12]. Lin HC et al tested the effect of the two probiotics Lactobacillus acidophilus and Bifidobacterium infantis (Inforan) in very low birth weight (VLBW) infants, and reported reduction of NEC [13], but no one investigated the combination of L. Acidophilus, L. Casei and L. Rhamnosus together. It seems that, probiotics if combined, will enhance or augment effects of each others. This is supported by the observation of Abrahamsson TR who reported that not all strains of probiotics are effective in preventing NEC in preterm infants [14], and, it explains the negative results encountered by some researchers (15). The observations from this study is in agreement with the findings by Alfaleh K and Anabress J, who searched 24 trials on probiotics effect in premature infants to conclude that the oral probiotics prevent severe NEC and all cause mortality in preterm infants [8]. The findings are also in agreement with Yang Y et al, who concluded in their meta analysis search on: probiotics in preventing NEC in preterms that: probiotic supplementation could significantly reduce the risk of NEC in preterm infants, regardless of gestational age and NEC stage, and did not increase the risk of sepsis or mortality, probiotic supplementation may have no adverse effect on normal feeding and growth [16]. Finally, this study finding and many others [17], strongly support and ringing the bell for us to consider probiotics as part of routine care for preterm infants in our neonatal units, especially in the third world, were both mortality and morbidity are high, yet we need to investigate the most effective preparation and combination and dose of probiotics.

5. CONCLUSION

This innovative intervention is significantly decreased the mortality (5.4% versus 21%, $p = < 0.02$) and morbidity (5.4% versus 52.6 %, $p < 0.03$), and decreased the mean time to discharge (13.4 days versus 27.2 days, $p < 0.05$), and almost abolished feeding intolerance. The drug in this combination and this dose, is well tolerated, has no adverse effect, no nosocomial infection is reported during the period of study, and is significantly shorten the hospitalization period, so it contributed to lessen the burden and expenses on both hospital and families.

RECOMMENDATIONS

- 1.This combined probiotics is proved its safety and usefulness in effectively preventing NEC, sepsis , feeding intolerance, and shorten hospitalization and enhancing wellbeing in preterm infants. So is recommended to be generalized in all neonatal units across the country.
- 2.Though this dose is safe and effective, yet the appropriate dose for preterm needs to be investigated and adjusted.
- 3.We need a ready to use probiotics solution in our country, I request Vitane Company to lead such a work for preterm neonates and young children.

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CONFLICT OF INTEREST

I disclose no conflict

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