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Randomized Control Trial of Probiotics in Prevention of Sepsis & Necrotizing Enterocolitis in Low Birth Weight Babies

KEYWORDS

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ABSTRACT *This Randomized control trial was conducted among 69 Low birth weight neonates(35 in study group & 34 in control group) admitted in NICU over a period of 2 years, to evaluate the role of probiotics in the prevention of sepsis & Necrotizing Enterocolitis in Low Birth Weight babies. The mean gestational age in the study group was 33.37+/-1.85 while in the control group was 33.21 +/-1.81.Babies had an average birth weight of 1.509 Kg in the study group and 1.564 kg in the control group. In this study, of the 69 babies enrolled,8.51% in the study group had sepsis while 8.82% in the control group development sepsis . No baby in either group had NEC and no baby in either group had feed intolerance. This study showed no statistical significance in the incidence of sepsis/ NEC between the study and the control groups.*

INTRODUCTION

In India sepsis is responsible for 36% of deaths. Neonatal sepsis among preterm babies is 64% of all babies with sepsis. As Per National Neonatal Perinatal Database (NNPD) 2002-2003, the incidence of neonatal sepsis in India was 30 per 1000 live birth. It is 3% among intramural babies and 39.7% among extramural admissions. Septicemia/meningitis accounts for 18.6% of neonatal deaths[1]. Although improvements in neonatal intensive care have decreased the impact of early-onset sepsis (EOS) in term infants, preterm infants remain at high risk for both EOS and its sequelae.

The incidence of late-onset sepsis was higher in Asia than in resource-rich countries. Mortality from neonatal sepsis was 10.4%, with an incidence of 0.69 deaths/1000 live births[33].

The incidence of Necrotizing enterocolitis is variable among different centres and even in a given centre its occurence varies from time to time depending on bacterial ecology of NICU, feeding practices,obstetric resuscitation procedures. There are endemic and epidemic occurrences. In most centers, NEC occurs in 2% to 5% of all NICU admissions and 5% to 10% of very low birth weight (VLBW) infants. If VLBW infants who die early are excluded and only infants who have been fed included, the incidence is approximately 15%.The overall incidence varies between1-2/1000 live births[2] .The overall mortality is 9% to 28% regardless of surgical or medical intervention. The mortality for infants weighing<1,500 g can be as high as 45%; for those weighing<750 g, it may be much higher. The incidence of NEC in term infants is 1 in 20,000 live births. NEC in term infants is a different disease process compared to that in preterm infants, displaying a more definite association with splanchnic hypoperfusion.Neonatal sepsis among term babies is 36% and preterm babies 64% of all the babies with sepsis[4].

In developing countries the incidence of sepsis is high due to various reasons like Majority of the newborn are low birth weight and premature (33%)[6],Most of the deliveries are done at home by untrained dais[7],During the delivery the dais will not maintain aseptic precaution (5) cleans viz; clean hands, clean surface, clean cord, clean blade, and clean cord tie),Traditional practices like [7,8] giving prelacteals, application of cow dung to the cord, delayed initiation of breast feeds and not giving colostrums,Over crowding of NICU and understaffing may lead to increased rate of cross infections[5],The infection control measures are not properly followed due to inadequate resource [5] , compromised immunity, iatrogenic factors resulting in breaks in mucosal and skin barrier and also abnormal colonisation of gut,prolonged stay in NICU, use of antibiotics, reduced exposure to maternal microflora and infection control procedures like hand washing and sterile feeds lead to decreased exposure and thereby decreased colonization with normal commensals.

The fecal flora of a healthy adult may have 400 different bacterial strains compared to less than 20 in a preterm in NICU. These include staphylococcus aureus, klebsiella, enterococci, clostridia and yeast. This abnormal pattern of colonization and lack of microbial diversity in the bowel may contribute to the development of NNEC and sepsis. Hence colonization with desirable microflora may be beneficial in the reduction of sepsis/NEC in LBW babies. One way to encourage normal bowel colonization with desirable flora is through administration of probiotics. Hence this study was undertaken to evaluate the role of probiotics in the prevention of sepsis of NEC in LBW babies.

DEFINITION: A live microbial supplement which beneficially affects the host by improving its microbial balance [10].

CRITERIA FOR PROBIOTIC: Several criteria must be fulfilled to classify a micro organism as a probiotic [11] which includes Human origin,Non pathogenic properties,Resistance is technological process (viability in delivery vehicles),Stability in acid and bile,Adhesion to target epithelial tissue,Ability to persist within the gastro intestinal tract,Production of anti microbial substance,Ability to modulate the immune system,Ability to influence meta-

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bolic activities.

PROBIOTIC MICRO ORGANISMS:
Most commonly used probiotics are non pathogenic yeast such as Saccharomyces boulardi ,Lactic acid bacteria –Lactobacillus and Bifidobacterium sps.

GENERIC NAME	SPECIES	STRAIN	REF
1. Lactic acid bacteria	L. rhamnosus, L. reuteri L. acidophilus L. bulgaricus	ATCC 53103GG DSM 12246 LB Not specified	12-22 23,24 25,26 27-29
2. Bifidobacterium	B. Lactis B. Infantis	Not specified	27-29
3.Streptococcus	S. thermophilus-lactis	Not specified	29-30
Non lactic acid bacteria 1.Saccharomyces	S. boulardi	Not specified	31

AIM& OBJECTIVE:
To study the effect of oral Saccharomyces boulardii (Econorm) in prevention of Sepsis/NEC in low birth weight babies.

MATERIALS AND METHODS
Place of Study

The Neonatal Intensive Care Unit

Department of Pediatrics

SVS Medical College Hospital

Mahabubnagar.

Study Design
Randomized control trial .

Period of Study
The study was carried out between November 2012 to june 2014

Study Population
Inclusion Criteria:-
Babies are eligible for study if:

1. Birth weight <2 Kg.
2. No signs of Sepsis at 24 hours of life.
3. Gestational age<37 weeks.
4. Informed consent taken from parents.

Exclusion criteria:-
1. Major congenital Malformations.
2. Severe Birth Asphyxia.

After the patient's inclusion, they were randomized.

Sample Size
Neonates with birth weight less than 2kg who are admitted in NICU over study period of 2yrs form the study and control groups.

Randomization
The eligible babies were randomly assigned to study group and control group. Randomization was done using computer generated random sequence.

Method
Babies in the study group were given oral Saccharomyces boulardii (Econorm) in a dose of 250mg once a day for 7 days. The powder was mixed in 5cc of EBM/formula and administered to the baby by the nurse. Babies in the control group were given oral EBM/Formula(Placebo) once a day for 7 days.

Outcome
Primary outcome
Babv was considered to have sepsis if they had 2/more clinical features and 1 sepsis screen positivity.

NEC was considered to be present if baby had distension of abdomen/aspirate and stool for occult blood (or) blood positive, X-ray showing dilated bowel loops, thick walls (or) pneumotosis intestinals.

Secondary outcome
Mortality, duration of fluids, weight loss per day, feed intolerance and duration of hospital stay.

Statistical Analysis of Data:

Statistical Analysis of data is done by chi-square testing and other relevant tests were applied wherever necessary.

Monitoring
All enrolled babies were clinically monitored for signs of Sepsis every day at 6 hourly intervals.

Whenever baby had either signs of sepsis/NEC the following investigations were done CBP, ANC,CRP, micro ESR,Blood Culture, X-ray abdomen.

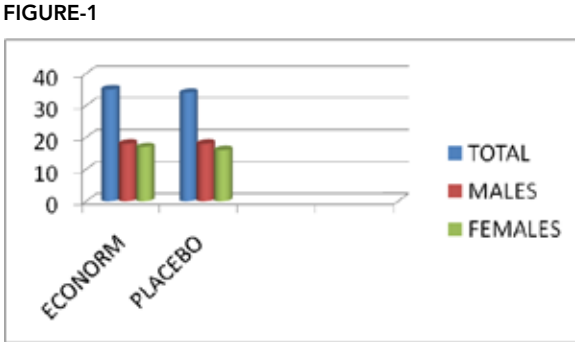
Management
Management of the baby was per unit protocols.

Babies were given feeds if they were clinically asymptomatic.

Feeds were increased every day 20ml/kg and IV fluids were stopped when the baby was tolerating 100 ml/kg/day of oral feeds.

RESULTS AND DISCUSSION
During the study period, a total of 69 babies were enrolled in the study.

FIGURE-1



35 babies were allocated to Econorm group and the rest

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34 to control group.

36 of the 69 babies enrolled were males.18 babies in each group were males.

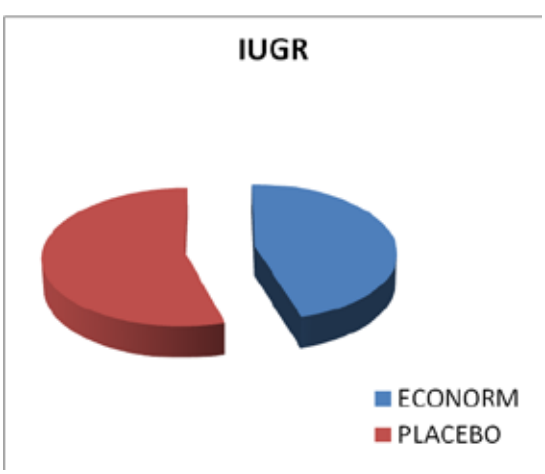
	ECONORM n=35	Placebo n=34	P value
MALES 36(52.2%)	18(51.4%)	18(52.9%)	
GEST AGE 33.28	33.37+/-1.85	33.21+/-1.81	0.708
BIRTH WT 1.536	1.509	1.564	0.335
<1.5KG 27 (39.13%)	16(45.71%)	11(32.35%)	
1.5.2 KG 42 (60.86%)	19(54.28%)	23(32.35%)	
LSCS 30(43.5%)	17(48.6%)	13(38.2%)	
PROM 1 (1.4%)	1(2.9%)	_	
IUGR 11(15.94%)	5(14.28%)	6(17.64%)	
PIH 27(39.13%)	15(42.8%)	12(35.29%)	
OLIGOHYDRAM-NIOS6(8.69%)	3(8.57%)	3(8.82%)	

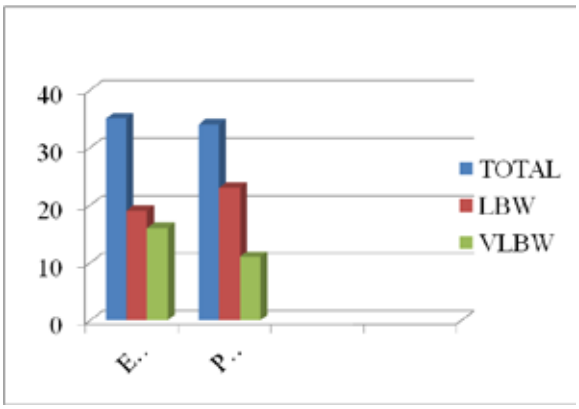
Mean gestational age was 33.28.The mean gestational age in the study group was 33.37+/-1.85 while in the control group was 33.21 +/-1.81.

LSCS was done in 48.6% in the study group while 38.39% of Mothers had PIH and 6 mothers had oligohydramnios.

Both the Econorm and the control group were comparable for Gestational age, Birth weight, Mode of delivery, Maternal PIH, oligohydramnios.

Out of the Total 69 babies, 11 babies were IUGR (5 in the study group were IUGR , 6 in the placebo group were IUGR). FIGURE-2





Mean birth weight was 1536 grams.

Babies had an average birth weight of 1.509 Kg. in the study group and 1.564 kg in the control group.

45.7% babies in the study group and 32.35% in the control group were < 1.5 Kg.

TABLE-2

	ECONORM	PLACEBO	P Value
CLINICAL SEPSIS 6(8.7%)	3(8.6%)	3(8.8%)	0.7
MORTALITY 6 (8.7%)	3(8.6%0	3(8.85)	
FLUIDS	3	3.6	
HOSPITAL STAY	6.71+/1.07	7.12+/1.27	0.16
WEIGHT LOSS PER DAY 0.031	0.030	0.032	
FEED INTOLER-ANCE	--------	--------	---------

TABLE-3

	CLINICAL FEATURES	CRP	ESR	TLC	ANC	PLC	BLOOD C / S
ECONORM	Lethargy, Tachy-cardia Prolonged CFT	12	12	10,200	2,856	1.3	Contaminate
	Lethargy, Tachycardia CFT	48	14	7,500	3450	2.4	No bacterial growth
	Dull, Sclerema, Prolonged CFT	30	12	8,660	3,464	2	Klebsiella

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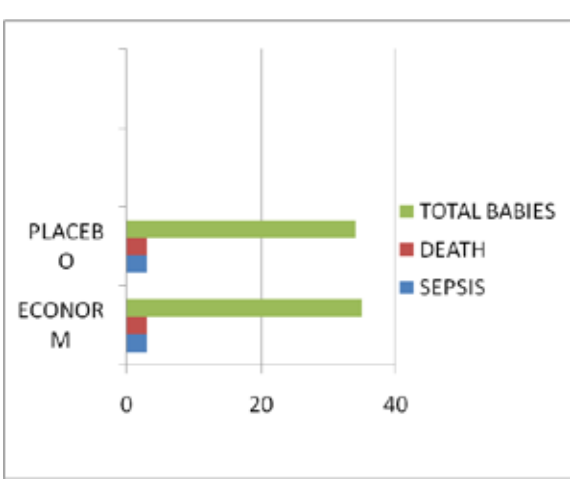
	Sclerema, Lethargy, Tachycardia	48	8	11,800	8,260	1.5	Klebsiella
PLACEBO	Lethargy, Tachycardia Prolonged CFT	36	16	12,500	6,552	2	No bacterial Growth
	Dull apnea, Lethargy	24	2	9,800	3,724	2.5	No bacterial Growth

TABLE-4

	CLINICAL PICTURE	INVESTIGATION			CAUSE OF DEATH
		CRP	Micro ESR	BloodC/s	
ECONORM	Lethargy, Tachycardia, Prolonged CFT	48	14	No bacterial growth	sepsis
	Apnea	----	-----	----	Apnea
	Dull, Prolonged CFT, Sclerema	30	12	Klebsiella	Sepsis
PLACEBO	Resp. Distress	(-ve)	6		HMD
	Lethargy,Tachycardia Prolonged CFT	36	16	Blood c/s No bacterial Growth	sepsis
	Apnea	----	------	-----	Apnea

3 babies in each group had sepsis. 3 babies in each group expired.

FIGURE-4



Both the groups are comparable for the incidence of sepsis & mortality.

No baby in either group had NEC and no baby in either group had feed intolerance. Duration of IV fluids was comparable in both the groups. Duration of hospitalization was 6.17+/-1.07 days in study group while it was 7.12+/-1.27 days in the control group (P=0.16).

Average weight losses per day were 30gm in Econorm group and 32 gms/day in placebo group.

DISCUSSION

In the study, of the 69 babies enrolled,8.51% in the study group had sepsis while 8.82% in the control group developed sepsis. None of the babies in either group had NEC. There is no statistical significance between the incidence of sepsis/NEC between the study and the control groups. This is very similar to another study by Carlo Danni[3] et al in which 4.7% babies in the study group as against 4.1% in the control group had sepsis while 1.4% babies in the study group and 2.8% babies in the control group had NEC both of which are not statistically significant.

In another study by Hung Chin Lin et al. [9] there was a significant reduction in the incidence of sepsis and NEC in probiotic group compared to control group (p value0.03) for sepsis as well as NEC).

A study by Hoyos AB [32] also showed statistically significant reduction in the incidence of NEC with oral administration of probiotics (p<0.002).

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Limitations of the study

In our study, Econorm was not effective in the prevention of Sepsis/NEC in low birth weight babies. The possible reason for lack of efficacy in our study could be:-

We chose a very low risk group for Sepsis (Baby had to be asymptomatic at enrolment) as seen by the low incidence of sepsis in the control group.

We were aggressive in feeding all the babies with EBM (Most babies received only EBM.

As we were aggressive in enteral feeding, the duration of IV fluids was brought down as the average duration of IV fluids was only 3 days.

61% of babies were >1.5 Kg.

Since the outcome which we were studying was seen in only a very few number of enrolled babies, we could not see the efficacy of econorm for the prevention of Sepsis/ NEC.

Looking at our data, it appears that a large number of low risk babies have to be enrolled to study the efficiency of Probiotics in each a group.

The choice of probiotic,dosage,frequency of dosing need to be discussed because each probiotic has variable rate of colonization.

The adverse effects of probiotic supplementation like probiotic associated sepsis could not be analyzed in this study.

NEC is a multifactorial disease.The other factors contributing to NEC could not be analyzed in this study.

CONCLUSION

In a low risk group oral Saccharomyces boulardii (Econorm) is not effective in the prevention of Sepsis/NEC in low birth weight babies.

RECOMMENDATIONS

Probiotics may offer potential benefits to premature infants.

We are still in early stages of understanding numerous interactions that occur between intestinal microflora and probiotics.

Probiotics offer three advantages over other proposed strategies in prevention of NEC.

First is, it is simple, noninvasive method to recreate natural normal intestinal microflora. Secondly it appears to be effective in preventing one of the major morbidities in low birth weight babies.

Thirdly, its safety record is better than the other aggressive modalities of intervention. Neverthless probiotics may offer a promising strategy in preventing NEC in premature infants.

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