

The PiPS (Probiotics in Preterm Infants Study) Trial – Controlling the Confounding Factor of Cross-contamination Unveils Significant Benefits

We read with interest the recent article by Probiotics in Preterm Infants Study (PiPS) group which reported no benefits from probiotic use [1]. In a telephonic survey of probiotic use in 58 tertiary neonatal units in United Kingdom in February 2014, it has been reported that 38% of units awaited the outcome of PiPS trial, only 12% had already implemented and rest were undecided [2].

Cross-contamination of the placebo group in neonatal trials of probiotics has been described before as well and this significantly underestimates the effectiveness of probiotics [3,4]. The current study also finds significant levels of cross-contamination in the placebo group; 20.5% at two weeks and then more than double (49%) at the end-point of study, that is 36 weeks post-menstrual age [1]. This introduces a significant bias that creeps inadvertently post-randomization, thereby conferring the benefits intended for the intervention group to the placebo group as well. Since the purpose of intervention is colonization of gut with the administered probiotic strain, the distinction between the intervention and the placebo groups that exists, at the start of the study becomes blurred due to this phenomenon of cross-contamination; thus, in effect, nullifying the outcome comparison between the original groups.

We feel that table 5 in the original article comparing the outcome between colonized and non colonized groups will be true representative of the intended benefits of intervention. It is reported in the article that there is a decrease in the sepsis, necrotizing enterocolitis and death rate in the colonized group that does not reach statistical

significance. We note that the denominator in the non colonized group ($n = 462$) is significantly lower than that in the colonized group ($n=724$). We have worked out a hypothetical analysis table after equalizing the denominator of both the groups by boosting up the number in the non-colonized group to 724 and recalculating the outcome in that group using the percent incidence reported (**Table I**). Statistical analysis of the said hypothetical groups unveils significant benefits for all the outcomes studied in the intervention group with the effects on NEC-reduction being the strongest. We have reported significant beneficial effects of routine supplementation of probiotic *Saccharomyces boulardii* in neonates of birth weight 1000g to 1999 g in a small study from a tertiary neonatal unit in Southern India recently [5].

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TABLE I HYPOTHETICAL ANALYSIS TABLE OF STUDY REPORTED IN REFERENCE 1

Outcome	Colonization with <i>Bifidobacterium breve</i> BBG 001				
	Yes (724)	No (724)*	RR (95% CI)	NNT (95% CI)	P value
Necrotizing enterocolitis	47 (9%)	94 (13%)	0.5 (0.36-0.7)	15.4 (10.5-28.9)	<0.001
Sepsis	67 (9%)	101 (14%)	0.66 (0.5-0.89)	21.3 (12.5-71)	0.006
Death before discharge home	24 (3%)	51 (7%)	0.47 (0.3-0.76)	26.8 (16.7-68.8)	0.002

*NNT: Numbers needed-to-treat, *Number in Non-colonized group boosted up to same as colonized group, percent incidence of outcome variables is the same as in the article.*