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ORIGINAL ARTICLE

A double-blinded randomized trial on growth and feeding tolerance with *Saccharomyces boulardii* CNCM I-745 in formula-fed preterm infants☆

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KEYWORDS
Feeding (in)tolerance;
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Preterm infant;
Probiotic;
Sepsis

Abstract
Objective: The use of probiotics is increasingly popular in preterm neonates, as they may prevent necrotizing enterocolitis sepsis and improve growth and feeding tolerance. There is only limited literature on *Saccharomyces boulardii* CNCM I-745 (*S. boulardii*) in preterm infants.
Method: A prospective, randomized, case-controlled trial with the probiotic *S. boulardii* (50 mg/kg twice daily) was conducted in newborns with a gestational age of 30–37 weeks and a birth weight between 1500 and 2500 g.
Results: 125 neonates were enrolled; 63 in the treatment and 62 in the control group. Weight gain (16.14 ± 1.96 *vs.* 10.73 ± 1.77 g/kg/day, $p < 0.05$) and formula intake at maximal enteral feeding (128.4 ± 6.7 *vs.* 112.3 ± 7.2 mL/kg/day, $p < 0.05$) were significantly higher in the intervention group. Once enteral feeding was started, the time needed to reach full enteral feeding was significantly shorter in the probiotic group (0.4 ± 0.1 *vs.* 1.7 ± 0.5 days, $p < 0.05$). There was no significant difference in sepsis. Necrotizing enterocolitis did not occur. No adverse effects related to *S. boulardii* were observed.
Conclusion: Prophylactic supplementation of *S. boulardii* at a dose of 50 mg/kg twice a day improved weight gain, improved feeding tolerance, and had no adverse effects in preterm infants >30 weeks old.

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PALAVRAS-CHAVE
(In)Tolerância de alimentação;
Crescimento;
Enterocolite necrosante;
Neonato prematuro;
Probiótico;
Sepse

Ensaio duplo-cego randomizado sobre crescimento e tolerância de alimentação com a *Saccharomyces boulardii* CNCM I-745 em neonatos prematuros alimentados com fórmula

Resumo

Objetivo: O uso de probióticos está cada vez mais popular em neonatos prematuros, já que podem prevenir a enterocolite necrosante (ECN) e a sepse e aumentar o crescimento e a tolerância de alimentação. Há apenas uma literatura limitada sobre a *Saccharomyces boulardii* CNCM I-745 (*S. boulardii*) em neonatos prematuros.

Método: Um ensaio de caso-controle prospectivo randomizado com o probiótico *S. boulardii* (50 mg/kg duas vezes por dia) foi realizado com recém-nascidos com idade gestacional de 30 a 37 semanas e peso ao nascer entre 1500 e 2500 g.

Resultados: Foram incluídos 125 neonatos, 63 no grupo de tratamento e 62 no de controle. O ganho de peso (16,14 ± 1,96 em comparação a 10,73 ± 1,77 g/kg/dia, $p < 0,05$) e a ingestão de fórmula com nutrição enteral máxima (128,4 ± 6,7 em comparação a 112,3 ± 7,2 mL/kg/dia, $p < 0,05$) foram significativamente maiores no grupo de intervenção. Assim que a nutrição enteral foi iniciada, o tempo necessário para atingir a nutrição enteral completa foi significativamente menor no grupo probiótico (0,4 ± 0,1 em comparação a 1,7 ± 0,5 dia, $p < 0,05$). Não houve nenhuma diferença significativa em sepse. Não ocorreu ECN. Não foi observado nenhum efeito colateral relacionado à *S. boulardii*.

Conclusão: A suplementação profilática de *S. boulardii* a uma dose de 50 mg/kg duas vezes por dia melhorou o ganho de peso, aumentou a tolerância de alimentação e não teve nenhum efeito colateral em neonatos prematuros >30 semanas de idade.

Introduction

The gastrointestinal (GI) barrier function, gut motility, mucosal immunity, and digestive/absorptive capacity are all significantly underdeveloped in the preterm neonate.[1] Preterm infants have an increased risk of poor growth, nosocomial infections, and necrotizing enterocolitis (NEC), and of developing a different intestinal microbiota than healthy breast fed infants.[1,2] The latter is related to a higher incidence of delivery through cesarean section, decreased exposure to maternal microbiota, increased exposure to organisms that colonize neonatal intensive care units (NICUs), antibiotics (multiple courses), and delay in enteral feeding.[3]

The role for probiotics in the care of preterm newborns is debated. Probiotics are defined as ''live microorganisms which, when administered in adequate amounts, confer a health benefit to the host''.[4] While reports of improved growth and a decreased incidence of NEC are enticing, many aspects on the mechanisms of action are still unclear.[5,6] Studies have used different strains and dosages, making it difficult to draw evidence-based conclusions.[5–7]

Until now, researchers often selected strains belonging to bacterial species naturally present in the intestinal flora, such as lactobacilli and bifidobacteria.[8] *Saccharomyces boulardii* CNCM I-745 (*S. boulardii*) is a probiotic yeast isolated from the peel of fruits such as lychees, growing in Indochina.[9] *S. boulardii* has been poorly studied in preterm and low birth weight infants. The objective of the present study was to asses if *S. boulardii* administered to formula-fed preterm newborns >30 weeks of gestational age would improve weight gain and clinical outcome.

Methods

Patient inclusion

Stable formula fed preterm neonates admitted to the NICU of the Shengjing Hospital of the China Medical University in Shenyang (China) were included in this prospective randomized controlled double-blinded study, performed from April to July 2013. Informed consent was obtained from the infants' parents/guardians. The study protocol was approved by the University Hospital Ethical Committee.

The sample size was calculated prior to the start of the study for a significance level of $p < 0.05$ (two-sided), with a power of 80% ($\beta = 0.2$) to estimate the needed sample size, and with a weight gain standard deviation of 9 g/day in both groups and a weight gain difference between the two groups of 5 g/day. This resulted in a sample size of 125 infants, considering a 20% drop out rate.

Inclusion and exclusion criteria

Inclusion criteria were hospital-born formula-fed infants with a gestational age of 30–37 weeks and a birth weight between 1500 and 2500 g.

Exclusion criteria were severe neonatal pathologies, such as severe birth complications, GI malformations,