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Original Article

Effect of Probiotics in Prevention of Neonatal Jaundice

Robabeh Mousavinejad Chenarani[1], Gholamali Maamouri[2], Ezzat Khodashenas[3*], Hassan Boskabadi[2], Elham Bakhtiari[4], Sheila Kianifar[1]

1. Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2. Neonatal Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3. Neonatal Research Center, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
4. Clinical Research Development Center, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Background: Jaundice is the most common problem among neonates. Although neonatal jaundice is highly prevalent in Iran and the prevention and treatment of this disease is incredibly important, few studies have been conducted on the effect of probiotics in the prevention of hyperbilirubinemia in Iran so far. Considering the contradictory results in this regard, this study was conducted to investigate the effect of probiotics in preventing jaundice among neonates.

Methods: The statistical population of this three-blinded clinical trial on the first of January 2021 consisted of 196 neonates who were divided into two groups of placebo and intervention. The neonates with a gestational age of more than 37 weeks, birth weight of more than 2,500 grams, and without risk factors for jaundice were included in the study after that the research objectives and procedures were explained to their parents and their informed consent was obtained. Patients were randomly divided into the intervention and placebo groups. The intervention group underwent treatment with probiotics (1010 Saccharomyces boulardii daily for 5 days), while the other group received treatment with a placebo. The level of bilirubin was measured with a skin bilirubin meter and, if necessary (i.e., bilirubin more than 15), a blood test was administered before the intervention and on the third and fifth days after the intervention. The effect of probiotics on jaundice was compared in the two groups.

Results: Based on the study results, the level of forehead and chest bilirubin was not significantly different between the study groups before the intervention and 3 and 5 days after the intervention (P> 0.05). In cases that skin bilirubin levels were higher than 15 on the fifth day ,the mean serum bilirubin level was obtained at 15.71±0.99 mg/dl and 17.42±1.17 mg/dl in the intervention and placebo group, respectively, which was statistically significant (P = 0.03).

Conclusion The results of this study showed that the use of Saccharomyces boulardi decreased the level of serum bilirubin (P=0.03).

Keywords: Jaundice, Neonate, Probiotic, Saccharomyces boulardii

Introduction

Almost all neonates experience a transient increase in serum bilirubin in the first week after birth; however, only 60% of them may be recognized (1). Neonatal hyperbilirubinemia refers to when the total serum bilirubin level of the neonate is more than five milligrams percent (86 µmol/l). Although this clinical jaundice occurs in approximately 60% of term neonates and in 80% of preterm neonates, among which very few cases may have a significant underlying disease (2). Neonatal hyperbilirubinemia most often occurs in the indirect type. This type of jaundice is highly toxic to neonates and can be physiological or pathological. Sometimes hyperbilirubinemia is a direct type, which is not toxic to newborns and is always pathological. If indirect hyperbilirubinemia is left untreated, it may lead to Kernicterus (3).

Bilirubin is also one of the final products of decomposition. Its clinical signs in neonates are due to the deposition of bilirubin in the brain, which causes temporary dysfunction or permanent damage to the brain. Kernicterus is a rare, however, serious complication of jaundice. Therefore, early detection of jaundice is of particular importance (4). Newborns are usually discharged within the first 24 h after birth; since

* *Corresponding author*: Ezzat Khodashenas, Neonatal Research Center, Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: 09153011056; Email: Khodashenase@mums.ac.ir

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no clinical signs of jaundice develop during this time, the prevention of encephalopathy and jaundice is based on the diagnosis of high-risk neonates and its rapid treatment. According to clinical guidelines, early detection of babies at risk for severe jaundice is recommended for timely and effective prevention of its consequences (5). Therefore, the American Academy of Pediatrics has recommended a follow-up visit for the newborns who are discharged within the first 48 h. This visit is determined between the first and third day after discharge. If a follow-up visit is not possible, the discharge will be delayed until the end of the risk period (i.e., days three to four) (5).

Perhaps the first step before the rapid diagnosis and treatment of this disease is the prevention of the development of this disease, which requires identifying the risk factors for jaundice in order to reduce the risk of jaundice by decreasing the risk factors. At present, phototherapy and blood exchange are the two main treatments for neonatal jaundice, which consequently, increases the length of hospitalization of neonates in the intensive care unit and the side effects of these treatments on newborns with jaundice (6).

Complementary therapies to prevent jaundice are important. The results of a number of studies on different populations around the world have shown the effect of probiotics on the treatment of jaundice. Probiotics are living organisms that exert beneficial effects on the health of the host by modulating the intestinal microbial flora. The probiotics that have been studied the most in various fields are lactic acid-producing bacteria, including Lactobacillus and Bifidobacteria species. The mechanisms of action in these organisms have been proposed to justify their preventive and therapeutic effects on human disease, including the production of bacterial inhibitory compounds, modulation of intestinal pH, blockade of bacterial binding sites, competition for nutrient uptake, and system strengthening. Safety pointed out (7, 8).

Saccharomyces boulardii is a non-pathogenic fungus that has been prescribed for the prevention and treatment of bacterial diarrhea for the past 30 years (9). The yeast has also been shown to be effective in gastrointestinal diseases in which the inflammatory aspect is more prevalent, suggesting the possibility of the probiotic interfering with cellular signaling pathways, which is common in numerous inflammatory diseases. Saccharomyces boulardii is widely used as a probiotic and is sometimes used as a dietary supplement (10).

Due to the high prevalence of neonatal jaundice in Iran and the high importance of prevention and treatment of this disease, so far, few studies have been conducted on the effect of probiotics in preventing hyperbilirubinemia in Iran. Due to the contradictory results obtained in this regard, this study was carried out to investigate the effect of probiotics in preventing jaundice among neonates. The current study examined the effect of Saccharomyces boulardii probiotic on the prevention of jaundice in term newborns.

Methods

This study was aimed to evaluate the effect of probiotics in preventing jaundice in term neonates. This clinical trial was performed on two groups in parallel and in three blinds. The patients were randomly divided into two groups, namely intervention and placebo. Randomization was performed using computer software. Blinding was performed at the level of patients, evaluators, and statistical analysts. A placebo that was highly similar to the original drug used to blind patients and evaluators. In order to blind the statistical analyst, the groups were provided with coded forms.

Neonates who were born in the hospital with a gestational age of more than 37 weeks, birth weight of more than 2,500 g, and without a risk factor for jaundice were included in the study after providing the explanation to parents and obtaining informed consent from them. On the other hand, exclusion criteria were neonatal sepsis, hospitalization, ABO or Rh incompatibility, ceramic hematoma, subgaleal hemorrhage, clinical suspicion of hypothyroidism, diabetic mother, overweight, and intrauterine infection.

This study was performed from January 2018 to May 2019 in the Department of Midwifery of Ghaem Hospital, Mashhad, Iran. Patients were divided into intervention and control groups. The intervention group received treatment with probiotics (1010 Saccharomyces boulardii daily for 5 days). The medications in this group were in the form of capsules and prepared by the bio-fermentation pharmaceutical company called Daily East located in Iran. In the placebo group, completely similar medications were administered to patients in capsule form (daily east).

The level of bilirubin was measured with a skin bilirubin meter and, if necessary (i.e., bilirubin more than 15), a blood test was administered before the intervention and on the third and fifth days after the intervention. The effect of probiotics on jaundice was compared in the two

groups. The parents and nurses were responsible for administrating the medications and were unaware of whether the treatment was a medication or a placebo. Variables, such as age, gender, blood type, gestational age, bilirubin level, bilirubin location, defecation frequency, and type of delivery were considered.

Statistical methods and sample size: The collected data were entered into and analyzed in SPSS 23 software using mean and standard deviation to describe quantitative data), frequency and frequency percentage to describe qualitative data, and repeated measure ANOVA to examine the trend of changes in a variable during the follow-up time. The relationship between qualitative variables was tested using the Chi-square test. A comparison of a quantitative variable between the two groups was performed by independent t-test. The p-values of < 0.05 were considered significant. The outcome used to determine the sample size was the percentage of neonatal jaundice (60%) (11). Therefore, the sample size in this study was determined at 98 cases for each group.

Initially, the research objectives and procedures were explained to all mothers. The information regarding the study conditions and how to follow up was provided in the consent form, which was studied and signed by the mothers. All participants were assured of anonymity and confidentiality in this study.

Results

A total of 196 patients were entered into this three-blind clinical trial and were divided into two groups of intervention and control (n=98 each). Regarding the male/female ratio, 50 (47.6%) and 55 (52.4%) subjects were male in the placebo and intervention groups, respectively. There was no statistically significant difference between the two groups based on the Chi-square test (P=0.47). The gestational age of patients was significantly higher in the intervention group than in the placebo group; accordingly, the mean scores of gestational age in the placebo and intervention groups were 38.5 and 39 weeks, respectively, (P=0.001). Other underlying findings, such as blood type, type of delivery, maternal age, and the number of pregnancies, were not statistically significant in the two groups (P>0.05).

Investigation of changes in forehead bilirubin levels: As shown in Figure 1, forehead bilirubin increased in both groups during the study period. The comparison of the bilirubin level before the intervention and control of the gestational age revealed that there was no significant difference between the two groups (P=0.7). Bilirubin levels were compared between the two groups at each time of measurement. None of the forehead bilirubin levels were significantly different between the two groups (P>0.05). For qualitative evaluation, the forehead bilirubin level was divided into three groups, namely less than 5, 5-10, and 10-15. The results of our study showed that the level of forehead bilirubin was not significantly different between the study groups in any of the studied periods, including before the intervention and 3 and 5 days after the intervention (P>0.05) (Table 1).

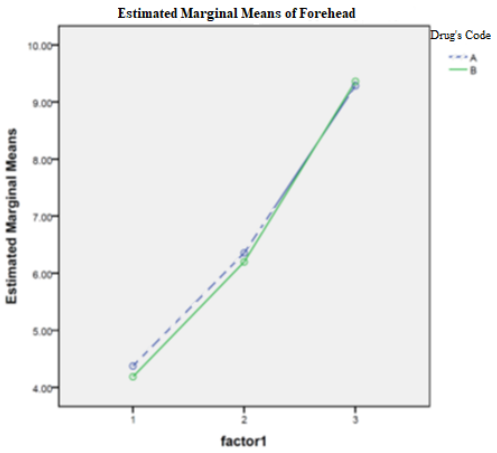

Figure 1. Comparison of forehead bilirubin changes in the intervention group (B) and placebo (A)

Table 1. Qualitative comparison of forehead bilirubin levels between study groups

	Forehead bilirubin level (mg/dl)	Placebo Group n (%)	Intervention group n (%)	*P-value
Before intervention	5<	73 (74.5)	77 (78.6)	0.50
	5-10	25 (25.5)	21 (21.4)	
	10-15	0	0	
3 days after intervention	5<	21 (21.4)	25 (25.5)	0.64
	5-10	72 (73.5)	70 (71.4)	
	10-15	5 (5.1)	3 (3.1)	
5 days after intervention	5<	1 (1.1)	2 (2.2)	0.65
	5-10	58 (61.7)	51 (56.0)	
	10-15	35 (37.2)	38 (41.8)	

*Friedman test

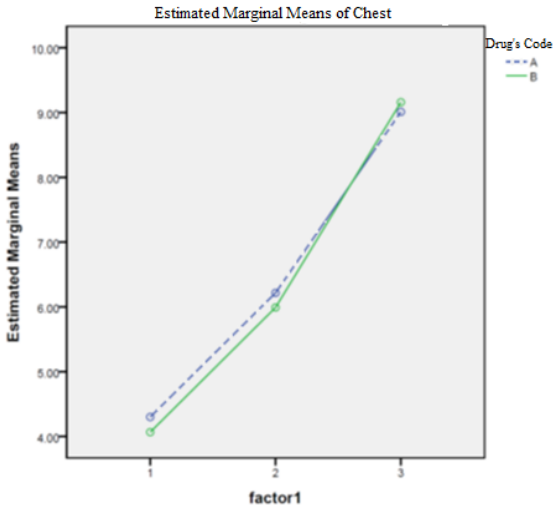

Figure 2. Comparison of chest bilirubin changes in the intervention group (B) and placebo (A)

Investigation of changes in chest bilirubin levels: The analysis of the trend of changes in chest bilirubin indicated that the level of chest bilirubin had a significant increase in each of the study groups during follow-up (P<0.001). However, by controlling bilirubin levels before the intervention and gestational age, no significant difference was observed between the two groups (P=0.71) (Figure 2). Chest bilirubin levels were assessed within 3 and 5 days after the intervention and there was no significant difference between study groups in any of the studied periods (P>0.05) (Table 2).

Investigation of changes in bilirubin levels in blood test: As mentioned, the bilirubin blood level was measured in the cases with the skin bilirubin level higher than 15 mg/dl. Skin bilirubin levels were higher than 15 only on the fifth day. The mean scores of serum bilirubin were 15.71±0.99 and 17.42±1.17 mg/dl in the intervention and placebo groups, respectively, which were statistically significant (P=0.03) (Table 3). In the intervention group, 2 (2%) cases received phototherapy indication, while in the placebo group, this number was 4 (4.1%). There was no significant relationship between the patient group and phototherapy (P=0.4, Chi-square test).

Investigating the trend of neonatal weight changes: The study of neonatal weight changes showed that although there was a significant increase in weight in each of the study groups during the follow up (P<0.05), with birth control and gestational age control, the trend of changes did not differ significantly between the two groups (P=0.34) (Figure 3). There was no significant difference in neonatal weight at birth and 3 and 5 days after the intervention (P>0.05).

The mean number of defecations was not significantly different between the two groups after 3 days (P=0.73). The mean frequency of defecation in a 5-day follow-up was 2.69±0.98 times in the placebo group and 2.21±1.06 times in the intervention group, which was statistically significant (P=0.001), meaning that defecation was significant in the last two days of follow up. Between the third and fifth days, the number of defecations was higher in the placebo group; nevertheless, in total, it was not significantly different in the two groups (P=0.12).

During the study, two cases in the intervention group developed gastrointestinal intolerance who were hospitalized on suspicion of neonatal infection. Nonetheless, after performing the necessary diagnostic measures, they were excluded from the study.

Table 2. Comparison of breast bilirubin levels between study groups

	Chest bilirubin level (mg/dl)	Placebo Group n (%)	Intervention group n (%)	*P-value
Before intervention	5<	65 (66.3)	70 (71.4)	0.44
	5-10	33 (33.7)	28 (28.6)	
	10-15	0		
3 days after intervention	5<	32 (32.7)	32 (32.7)	0.99
	5-10	60 (61.2)	60 (61.2)	
	10-15	6 (6.1)	6 (6.1)	
5 days after intervention	5<	10 (10.6)	1 (1.1)	0.02
	5-10	51 (54.3)	58 (63.7)	
	10-15	33 (35.1)	32 (35.2)	

*Chi-square test

Table 3. Comparison of serum bilirubin levels between study groups

	Intervention group n=4	Placebo Group n=7	P-value
Bilirubin level (mg/dl) 5 days after intervention	15.71±0.99	17.42±1.17	0.03

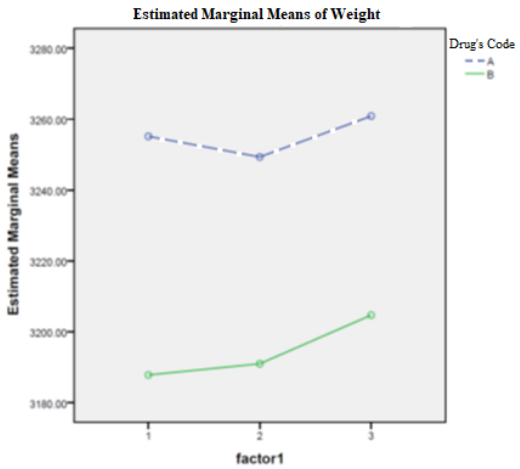

Figure 3. Comparison of birth weight changes in the intervention group (B) and placebo (A)

Discussion

This study aimed to evaluate the effect of Saccharomyces boulardii probiotic on the prevention of jaundice in 196 neonates. The neonates were assigned into two groups of intervention and control groups (n=98 each). Among these subjects, 50 (47.6%) and 55 (52.4%) cases were boys in the placebo and intervention groups, respectively. It was revealed that the gestational age was significantly higher in the intervention group than in the placebo group. Gender and other underlying findings, such as blood type, type of delivery, phototherapy, maternal age, and the number of pregnancies, were not statistically significant in the two groups. The trend of changes in forehead bilirubin increased during the study period; however, no statistically significant difference was observed between the two groups.

There were no significant differences between the two groups in any of the study periods, whether before the intervention or 3 or 5 days after the intervention. Considering the trend of changes in chest bilirubin, it was shown that although the level of chest bilirubin in each of the study groups had a significant increase during the follow-up, the trend of changes did not differ significantly between the two groups. Moreover, the level of chest bilirubin before the intervention, 3 and 5 days after the intervention were not significantly different between the two groups.

The study of the trend of changes in neonatal weight showed that although the weight had a significant increasing trend in each of the study groups during the follow-up, the trend of changes did not differ significantly between the two groups. Furthermore, the weight of the newborns at birth and 3 and 5 days after the intervention was not significantly different between the two groups. The mean number of defecations after 3 days was not significantly different between the two groups; nevertheless, on the fifth day, the mean frequency of defecation was significantly higher in the placebo group (there was no significant difference in the 5-day follow-up). In the study of changes in blood bilirubin level, the mean scores of serum bilirubin in the intervention and placebo groups were 15.71±0.99 and 17.42±1.17 mg/dl, respectively, which were statistically significant (P=0.03).

Demirel et al. (2012) conducted a study on 179 newborns weighing less than 1,500 grams or born under 32 weeks of age and assessed the effect of probiotics on the duration of phototherapy and their bilirubin levels. In the mentioned study, it was finally concluded that probiotic administration significantly could reduce the duration of hospitalization and intolerance to oral nutrition in newborns and did not have any side effects on them. However, probiotic administration in neonates lacked a direct effect on bilirubin levels, and the amount of bilirubin in the probiotic group was not significantly different from that in the control group (12).

In our study, the trend of changes in bilirubin and its values after 5 days of the study did not differ significantly between the study and control groups, which was consistent with the results of the study performed by Demiral et al. At the same time, the results of our study showed that in patients whose serum bilirubin level was higher than 15 mg/dL, the intervention group had significantly lower bilirubin than the placebo group after 5 days. However, the number of defecations was significantly lower in neonates who took probiotics than in the control group. Demiral et al. believed that considering the effects of probiotics on the normal intestinal flora, they decreased the absorption of bilirubin in the intestine and reduced the complications of jaundice. The main difference between our study and that of Demiral et al. was that our study was performed on normal-weight neonates, while Demiral et al. carried out a study on all newborns weighing less than 1,500 grams.

In another study conducted by Armenians et al. (2015) with the aim of investigating the effect of prebiotic on the management of low-birth-weight patients with hyperbilirubinemia, 25 infants were included in the study (13). In the mentioned study, in contrast to our study, bilirubin levels were

significantly reduced in the prebiotic group, and the neonates who took prebiotics had a significantly higher frequency of defecation than those in the control group. Additionally, the neonates in the prebiotic group needed less enteral nutrition than their counterparts in the control group. Finally, because of the benefits of prebiotic nutrition in newborns, Armenians et al. suggested that the prebiotic could be used to manage jaundice. In our study, probiotics rather than prebiotics were used. Prebiotics are fibers and substances that promote the growth of beneficial bacteria in the gut. The results of our study were inconsistent with those of the study conducted by Armenians et al. In our study, bilirubin levels were not different in the control group and the probiotic group. The study of Armenians et al. was performed on low birth weight patients, while our study was carried out on normal weight neonates (13).

In a study conducted by Turkmen et al. (2016) on reducing the length of hospitalization in patients with jaundice, 92 neonates were included in the study (10). The findings of the mentioned study, which was conducted as a randomized clinical trial, showed that as in our study, bilirubin levels in the control and probiotic groups were not significantly different from each other; nevertheless, the duration of hospitalization was significantly shorter in the probiotic group than in the control group. In our study, the length of hospital stay was not evaluated, nonetheless, the rate of defecation was significantly lower in the probiotic group than in the control group (10).

Soganti et al. (2013) performed a study on 181 healthy and term neonates (14) to evaluate the effect of Saccharomyces boulardii probiotic on the treatment of jaundice in term neonates. The findings of this study, which was methodologically the closest study to ours, showed that on the third day of the study, both in patients with and without clinical jaundice, bilirubin levels were significantly lower than those in the control group. These results were inconsistent with those of our study since in our study, on both the third and fifth days of the study, there was no significant difference between the control group and the probiotic group. However, our results on day 5 of follow-up showed that the effect of probiotics on the need for phototherapy was significantly lower in patients with bilirubin levels greater than 15 mg/dL than in the control group. The similarities between our study and the study conducted by Sougani et al. are the type of study design and the participants entered into the study (14).

In a randomized clinical trial study conducted by Liu et al. (2015) on 68 full-term neonates, the effect of probiotics, including Bifid Triple Viable, was evaluated on neonatal jaundice. Accordingly, bilirubin levels were evaluated before the intervention and 1, 4, and 7 days after probiotic treatment in neonates. The results of the study showed that the levels of bilirubin were not different in the control and case groups from each other before the study and 1 day after treatment; nevertheless, after 4 and 7 days after treatment, Bifid Triple Viable was significantly less in the probiotic group than in the control group. In addition, the duration of jaundice and phototherapy was significantly shorter in the probiotic group than in the control group. However, in qualitative comparison of chest bilirubin levels on the third to fifth day, bilirubin levels in the intervention group were significantly lower. Moreover, other variables, such as the duration of jaundice and the amount of phototherapy, were not studied in our study (15).

A systematic review study was conducted by Dashmach et al. (2017) to investigate the effect of probiotics on the management of jaundice. They indicated that probiotics reduced the duration of phototherapy in newborns (16). A significant decrease was observed after 3 days in the case group; nonetheless, probiotics could not significantly reduce the incidence of jaundice in neonates, in comparison to the control group. Finally, this study suggested that probiotics might reduce the duration of phototherapy; however, they failed to reduce the incidence of jaundice and could not be used as a routine method to prevent jaundice. In our study, probiotics did not significantly reduce bilirubin, compared to the control group, which was inconsistent with the results of the mentioned study, in which, probiotics did not reduce the incidence of jaundice (16).

Recently, Sainan Fan et al. (2021) has reported that phototherapy can significantly affect intestinal probiotics and metabolic parameters in neonates with jaundice, which may contribute to the side effects of phototherapy. The aforementioned study focuses on changes in intestinal probiotic strains and metabolism in newborns undergoing phototherapy and has indicated that phototherapy can significantly reduce important probiotics in the body and affect bile acid metabolism. Accordingly, there is no standard determined for the selection of a specific probiotic in neonates with jaundice that receive treatment with phototherapy; therefore, this

study is the theoretical basis for suggesting a probiotic that effectively reduces the side effects of phototherapy (17).

Nowadays, the use of probiotics in the treatment of various diseases is discussed. The current study was conducted due to conflicting results regarding the employment of probiotics in the prevention or improvement of hyperbilirubinemia in neonates. The findings of this study indicated that the use of probiotics was not effective in preventing jaundice in neonates; however, it reduced the need for phototherapy, compared to the placebo group, which decreased the need for hospitalization for phototherapy and its complications. In this respect, it can be used to reduce the intensity of jaundice.

One of the strengths of our study was that it was a study that investigated the effect of probiotics on neonatal jaundice for the first time in healthy Iranian neonates. The sample size of our study consisted of 196 newborns, which was a high sample size compared to similar studies.

Conclusion:

Due to the conflicting research on the use of probiotics in the prevention or treatment of elevated blood bilirubin in neonates, our study aimed to investigate the effect of Saccharomyces boulardii probiotics in the prevention of jaundice in term healthy neonates without any risk factors. The results of this study showed that the use of Saccharomyces boulardii was not effective in preventing jaundice in neonates; nevertheless, it decreased the need for phototherapy as a treatment for jaundice, and therefore, reduced the necessity of hospitalization and other complications that were related to it. It is recommended to conduct further studies in this regard with other kinds of probiotics or higher daily dosages.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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