

Clinical Trial Protocol

Iranian Registry of Clinical Trials

18 Jun 2026

Investigating the effect of probiotic supplements on hyperbilirubinemia in term neonates

Protocol summary

Study aim

Determining the effect of probiotic supplements on hyperbilirubinemia in term neonates

Design

A double-blind three-arm parallel group randomized phase 3 clinical trial with a control group of 81 patients.

Settings and conduct

Neonates with hyperbilirubinemia hospitalized at Shahid Beheshti Hospital in Kashan will be included in the study. Patients will be assigned into three groups receiving placebo, Reuteflor, or Ramnoflor. Outcomes will be evaluated at the beginning of the intervention and after 24, 48, 72, and 96 hours. Researchers and participants will be blinded to the type of intervention.

Participants/Inclusion and exclusion criteria

Inclusion criteria: 1) 35 to 42 weeks of gestation 2) Birth weight between the 10th and 90th percentile 3) Newborns aged from birth to 14 days 4) Hyperbilirubinemia based on Bhutani Nomogram
Exclusion criteria: 1) Unwillingness to cooperate (lack of parental consent) 2) Taking antibiotics 3) Any acute or active infection 4) Occurrence of any side effects 5) Not consuming breast milk exclusively 6) Thyroid disorders 7) Presence of respiratory distress 8) NICU admission 9) Congenital heart disease 10) The presence of hemolysis, hemoglobinopathies, and hemolytic blood diseases such as G6PD deficiency, blood group incompatibility 11) Cephal hematoma and subgaleal hemorrhage 12) Phenobarbital consumption by the mother in the last month of pregnancy 13) Non-physiological hyperbilirubinemia 14) Presence of a life-threatening congenital disorder 15) Blood exchange 16) Outpatient treatment

Intervention groups

Patients will be assigned to three groups receiving Ramnoflor (n=24), Reuteflor (n=24) or placebo (n=33). Once daily and each time 5 drops of Ramnoflor (Lactobacillus Rhamnosus) or Reuteflor (Lactobacillus Reuteri) or placebo will be given to each group,

respectively.

Main outcome variables

Total bilirubin; Direct bilirubin; Indirect bilirubin

General information

Reason for update

Acronym

IRCT registration information

IRCT registration number: **IRCT20230816059167N1**

Registration date: **2023-08-21, 1402/05/30**

Registration timing: **prospective**

Last update: **2023-08-21, 1402/05/30**

Update count: **0**

Registration date

2023-08-21, 1402/05/30

Registrant information

Name

Fatemeh Rahemi

Name of organization / entity

Country

Iran (Islamic Republic of)

Phone

+98 31 5546 1276

Email address

rahemi-f@kaums.ac.ir

Recruitment status

Recruitment complete

Funding source

Expected recruitment start date

2023-08-23, 1402/06/01

Expected recruitment end date

2023-10-22, 1402/07/30

Actual recruitment start date

empty

Actual recruitment end date

empty

Trial completion date
empty

Scientific title
Investigating the effect of probiotic supplements on hyperbilirubinemia in term neonates

Public title
Investigating the effect of probiotics on neonatal jaundice

Purpose
Treatment

Inclusion/Exclusion criteria
Inclusion criteria:
35 to 42 weeks of gestation Birth weight between 10th and 90th percentile Newborns aged from birth to 14 days Hyperbilirubinemia based on Bhutani Nomogram
Exclusion criteria:
Unwillingness to cooperate (lack of parental consent) Taking antibiotics Any acute or active infection Occurrence of any side effects Not consuming breast milk exclusively Thyroid disorders Presence of respiratory distress NICU admission Congenital heart disease The presence of hemolysis, hemoglobinopathies, and hemolytic blood diseases such as G6PD deficiency, blood group incompatibility Cephal hematoma and subgaleal hemorrhage Phenobarbital consumption by the mother in the last month of pregnancy Non-physiological hyperbilirubinemia Presence of a life-threatening congenital disorder Blood exchange Outpatient treatment

Age
From **1 day** old to **14 days** old

Gender
Both

Phase
3

Groups that have been masked

- Participant
- Care provider
- Investigator
- Outcome assessor

Sample size
Target sample size: **81**

Randomization (investigator's opinion)
Randomized

Randomization description
In order to randomly allocate patients among groups, first, the table of random numbers is extracted from the Stattrek website (<https://stattrek.com/statistics/random-number-generator.aspx>) and then these numbers are assigned to groups using the block randomization method.

Blinding (investigator's opinion)
Double blinded

Blinding description
All three drops of Ramnoflor, Reuteflor, and placebo received from Fara Daru Fanavar Mehr (Farabiotic) company and prepared in packages with the same appearance and are coded (A, B, or C) by individuals who

have no role in the study. During the study, the parents of the studied neonates and the researchers are blinded to the type of intervention.

Placebo
Used

Assignment
Parallel

Other design features

Secondary Ids
empty

Ethics committees

1

Ethics committee
Name of ethics committee
Ethics committee of Kashan University of Medical Sciences
Street address
Kashan University of Medical Sciences, Pezeshk Boulevard, Ghotbe Ravandi Boulevard, Kashan
City
Kashan
Province
Isfahan
Postal code
8715988141

Approval date
2023-07-16, 1402/04/25

Ethics committee reference number
IR.KAUMS.MEDNT.REC.1402.093

Health conditions studied

1

Description of health condition studied
Neonatal hyperbilirubinemia

ICD-10 code
P59.9

ICD-10 code description
Neonatal jaundice, unspecified

Primary outcomes

1

Description
Total Bilirubin

Timepoint
At the beginning of the study and 24, 48, 72 and 96 hours after the intervention

Method of measurement
Serum total bilirubin (mg/mL)

2

Description
Direct Bilirubin

Timepoint

At the beginning of the study and 24, 48, 72 and 96 hours after the intervention

Method of measurement

Serum direct bilirubin (mg/mL)

3

Description

Indirect Bilirubin

Timepoint

At the beginning of the study and 24, 48, 72 and 96 hours after the intervention

Method of measurement

Serum indirect bilirubin (mg/mL)

Secondary outcomes

1

Description

Length of hospital stay

Timepoint

At the time of discharge

Method of measurement

Days

2

Description

Defecation

Timepoint

on a daily basis from the day the intervention started until 96 hours later

Method of measurement

Number of defecations per day

3

Description

Complications including allergic reactions, gastrointestinal complications and ...

Timepoint

on a daily basis from the day the intervention started until 96 hours later

Method of measurement

History taking and physical examination

Intervention groups

1

Description

1st Intervention group: Once daily and each time 5 drops of probiotic supplement containing Lactobacillus Reuteri prepared by Fara Daru Fanavar Mehr (Farabiotic) pharmaceutical company under the brand name Reuteflor. Each 5 drops of Reuteflor contains $8 \times (10^8)$ lyophilized active cells of Lactobacillus Reuteri. This drop does not contain ingredients of mother's milk.

Category

Treatment - Drugs

2

Description

2nd Intervention group: Once daily and each time 5 drops of probiotic supplement containing Lactobacillus Rhamnosus prepared by Fara Daru Fanavar Mehr (Farabiotic) pharmaceutical company under the brand name Ramnoflor. Each 5 drops of Ramnoflor contains $8 \times (10^8)$ lyophilized active cells of Lactobacillus Rhamnosus. This drop does not contain ingredients of mother's milk.

Category

Treatment - Drugs

3

Description

Control group: Once daily and each time 5 drops of the placebo drop containing the base composition of probiotic drops without active ingredients. Placebo drops prepared by Fara Daru Fanavar Mehr (Farabiotic)

Category

Placebo

Recruitment centers

1

Recruitment center

Name of recruitment center

Shahid Beheshti Hospital, Kashan

Full name of responsible person

Seyyed Ramin Madani

Street address

Shahid Beheshti Hospital, Ghotbe Ravandi Boulevard, Kashan

City

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Province

Isfahan

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8115187159

Phone

+98 31 5554 0026

Email

drraminmadani@gmail.com

Sponsors / Funding sources

1

Sponsor

Name of organization / entity

Kashan University of Medical Sciences

Full name of responsible person

Gholam Ali Hamidi

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Kashan University of Medical Sciences, Pezeshk Boulevard, Ghotbe Ravandi Boulevard, Kashan

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Phone
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Email
hamiidi@yahoo.com
Grant name
Grant code / Reference number
Is the source of funding the same sponsor organization/entity?
Yes
Title of funding source
Kashan University of Medical Sciences
Proportion provided by this source
50
Public or private sector
Public
Domestic or foreign origin
Domestic
Category of foreign source of funding
empty
Country of origin
Type of organization providing the funding
Academic

2

Sponsor
Name of organization / entity
Fara Daru Fanavar Mehr (Farabiotic)
Full name of responsible person
Ali Keyvani
Street address
No. 1462, North Kargar st., Pharmaceutical Incubators Center, Tehran, Iran
City
Tehran
Province
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Postal code
1439955991
Phone
+98 21 8835 9880
Fax
Email
info@farabiotic.com
Web page address
https://farabiotic.com/fa_ir/
Grant name
Grant code / Reference number
Is the source of funding the same sponsor organization/entity?
Yes
Title of funding source
Fara Daru Fanavar Mehr (Farabiotic)
Proportion provided by this source
50
Public or private sector
Private
Domestic or foreign origin
Domestic
Category of foreign source of funding

empty
Country of origin
Type of organization providing the funding
Industry

Person responsible for general inquiries

Contact
Name of organization / entity
Kashan University of Medical Sciences
Full name of responsible person
Seyyed Ramin Madani
Position
Assistant Professor
Latest degree
Subspecialist
Other areas of specialty/work
Pediatrics
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Person responsible for scientific inquiries

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Other areas of specialty/work
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Person responsible for updating data

rahemi-f@kaums.ac.ir

Contact

Name of organization / entity

Kashan University of Medical Sciences

Full name of responsible person

Fatemeh Rahemi

Position

Resident

Latest degree

Medical doctor

Other areas of specialty/work

Pediatrics

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Email

Sharing plan

Deidentified Individual Participant Data Set (IPD)

Undecided - It is not yet known if there will be a plan to make this available

Study Protocol

Undecided - It is not yet known if there will be a plan to make this available

Statistical Analysis Plan

Undecided - It is not yet known if there will be a plan to make this available

Informed Consent Form

Undecided - It is not yet known if there will be a plan to make this available

Clinical Study Report

Undecided - It is not yet known if there will be a plan to make this available

Analytic Code

Undecided - It is not yet known if there will be a plan to make this available

Data Dictionary

Undecided - It is not yet known if there will be a plan to make this available