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

Isfehan

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 8x(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 8x(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
Kashan
Province
Isfehan
Postal code
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
Street address
Kashan University of Medical Sciences, Pezeshk Boulevard, Ghotbe Ravandi Boulevard, Kashan
City
Kashan
Province

Isfehan

Postal code

8715981151

Phone

+98 31 5554 2999

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

Tehran

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

Street address

Shahid Beheshti Hospital, Ghotbe Ravandi Boulevard, Kashan

City

Kashan

Province

Isfehan

Postal code

8115187159

Phone

+98 31 5554 0026

Email

drraminmadani@gmail.com

Person responsible for scientific 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

Street address

Shahid Beheshti Hospital, Ghotbe Ravandi Boulevard, Kashan

City

Kashan

Province

Isfehan

Postal code

8115187159

Phone

+98 31 5554 0026

Email

drraminmadani@gmail.com

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

Street address
Shahid Beheshti Hospital, Ghotbe Ravandi Boulevard, Kashan

City
Kashan

Province
Isfehan

Postal code
8115187159

Phone
+98 31 5554 0026

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