Review Paper

Effects of Dextrose Gel in Preventing and Treating Neonatal Hypoglycemia: A Systematic Review and Meta-analysis

Moloud Fakhri[1*], Roya Farhadi[2], Seydeh Sedigheh Yousefi[3], Mahmood Moosazadeh[4], Melina Ramezanpour[5], Mohammad Azadbakht[6]

1. Traditional and Complementary Medicine Research Center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran.
2. Pediatric Infectious Diseases Research Center, Mazandaran University of Medical Sciences, Sari, Iran.
3. Department of Traditional Persian Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
4. Gastrointestinal Cancer Research Center, Non-communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.
5. Department of Medical, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
6. Traditional and Complementary Medicine Research Center, Addiction Institute, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.

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ABSTRACT

Neonatal hypoglycemia is one of the major complications in neonatal wards, requiring rapid diagnosis and treatment to prevent its complications. Dextrose gel is used as a cheap and safe choice. Thus, the present systematic review and meta-analysis study aimed to investigate the effects of oral dextrose gel in preventing and treating neonatal hypoglycemia. To find the relevant articles, the national databases, including Barekat Gostar, SID, Magiran, IranDoc, and international databases, including PubMed, Scopus, Web of Science, Cochrane, and Google Scholar were consulted with standard keywords. The data were analyzed using the STATA 14 software, while the P value < 0.05 was considered significant. In 9 articles with a sample size of 8755 neonates, the mean neonatal weight ranged from 2890 to 3669 g. The share of neonates born through normal vaginal delivery equaled 61%, while 16% had low birth weight (below 2500 g), 16% had high birth weight (above 4500 g), 51% had diabetic mothers, 20% were premature, and 88% were singleton. Oral dextrose gel reduced the risk of neonatal hypoglycemia by OR=0.83 (95% CI: 0.75-0.93). However, neonatal hypoglycemia treatment with oral dextrose gel had an OR=0.78 (95% CI: 0.57-1.07), which was not statistically significant. Oral dextrose gel was effective in preventing neonatal hypoglycemia.

** Corresponding Author:*
Moloud Fakhri, Assistant Professor.
Address: *Mazandaran University of Medical Sciences, Mazandaran, Iran.*
Tel: *+98 (911) 1520601*
E-mail: *mmfir@yahoo.com*

1. Introduction

Neonatal hypoglycemia is the most common metabolic disorder among neonates (1), affecting 15% of newborn neonates (2) and 50% of high-risk neonates (premature, diabetic mothers, low or high birth weight) (3). Moreover, the rate of neonatal hypoglycemia is growing because of the increased rate of premature delivery (3) and maternal factors, such as diabetes (4) and obesity (5) which predisposes neonates to hypoglycemia.

Neonatal hypoglycemia is associated with brain damage, seizure, mental retardation, and death. Thus, early diagnosis and screening of endangered neonates are highly important in many countries to prevent the perilous complications of neonatal hypoglycemia (6-8). Currently, no strategy is available other than early breastfeeding to prevent neonatal hypoglycemia (9). However, many neonates may not maintain normal blood glucose levels only by breastfeeding and require intravenous dextrose (10).

Therapeutic choices are different based on the neonate's birth weight and gestational age (11). Dextrose gel 40% is among the therapeutic choices (12). The first line of treatment for neonatal hypoglycemia is a combination of breastfeeding and dextrose gel; in case of treatment failure, the neonate will need intravenous dextrose, which requires admission to the neonatal intensive care unit (NICU) (13). As an affordable and safe choice for the neonatal population (14, 15), dextrose gel reduces the use of IV dextrose NICU admission because of hypoglycemia, mother and neonate separation, and hospital costs, and improves breastfeeding rate (14, 16).

Several studies have been conducted on the use of dextrose gel for the prevention and treatment of neonatal hypoglycemia. As these studies have reported controversial findings, the present systematic review and meta-analysis study is conducted to investigate the effect of dextrose gel in preventing and treating neonatal hypoglycemia to provide an overall estimate of the published articles up to now. The present study is the first meta-analysis on both prevention and treatment investigating the relationship between oral dextrose gel and neonatal hypoglycemia.

2. Materials and Methods

Study protocol

The present study is a systematic review and meta-analysis in which the effects of oral dextrose gel on the prevention and treatment of neonatal hypoglycemia is investigated. The present study is written based on the PRISMA statement on the systematic review and meta-analysis studies.

Study outcomes

The primary outcome of this article can be summarized as follows: determining the relationship between the consumption of oral dextrose gel on the blood glucose level of neonates (relative risk or odds ratio).

Search strategy

In the present meta-analysis, the national databases, including Barekat Gostar, SID, Magiran, IranDoc, and international databases, including PubMed, Scopus, Web of Science, Cochrane, and Google Scholar were consulted without time or language limitations. The full-text articles in languages other than Persian and English were translated to extract the required data. The search was done using valid and standard keywords: "Dextrose gel," "Prevention," "Therapy," "Hypoglycemia," "Infant," and "Newborn." The Persian equivalents and MeSH terms of keywords were also applied (updated on 13.12.2021). Moreover, the combinations of the keywords were searched using "AND, OR" operators. Moreover, the reference list of all primary studies left at the end of the PRISMA flowchart and included in the meta-analysis was searched manually.

Study inclusion and exclusion criteria

PICO Elements

The PICO elements were defined as follows: population: a group of neonates who received oral dextrose gel; intervention: oral dextrose gel; comparison: a group of neonates who did not receive oral dextrose gel or received placebo; and, outcome: prevention and treatment of neonatal hypoglycemia.

Inclusion criteria

Clinical trials and cohort studies on the effects of oral dextrose gel on neonatal hypoglycemia were included in this meta-analysis. The intervention group received

oral dextrose gel while the control group received either no intervention or a placebo.

Exclusion criteria

The exclusion criteria comprised the following items: qualitative studies on the effects of oral dextrose gel on neonatal hypoglycemia, low-quality studies based on Cochrane and STROBE quality checklists, case report studies, studies not reporting the required data for statistical analysis, studies on the effect of intravenous dextrose on the neonatal hypoglycemia, and studies with inaccessible full-text.

Studies' quality assessment

The quality of the studies was assessed using a standard STROBE checklist (17). The STROBE checklist includes 22 items covering different parts of a report. The maximum STROBE score is 44: a score of 1-15 reflects poor quality, 16-30 reflects medium quality, and 31-44 reflects high quality. The cut-off score for the present study was 15, although all included studies had high quality.

The Cochrane collaboration checklist for assessing the risk of bias in randomized trials was utilized for the clinical trials (18). This checklist consists of 7 items, each assessing one dimension or important bias types in clinical trials. Moreover, each checklist item has 3 choices: high bias risk, low bias risk, and unknown. After examining the risk of bias in all studies, the discrepancy items were evaluated in each study and turned to the same choice by both investigators.

Data extraction

Two researchers extracted the data independently to minimize the reporting bias and data collection errors. The researchers entered the data into a checklist, consisting of the authors' names, publication year, study title, sample size, birth weight, mother's age, neonate's age, mother's BMI, ethnicity, and so on. The third researcher investigated the extracted data by the other two researchers and resolved the discrepancies. If the required data was not reported in the primary studies, the corresponding author was contacted via email and was asked for the required data, repeated up to 3 times (at least every 5 days) if not answered.

Statistical analysis

Odds ratio (OR) was used to investigate the effects of oral dextrose gel on neonatal hypoglycemia compared to the control group. To combine the results of the studies, OR logarithm was used in each study. Moreover, the I2 index and Q-Cochrane test were used to assess the heterogenicity between the studies. The I2 index is classified as low (I2<25%), medium (25%<I2<50%), and high heterogenicity (I2>75%). The fixed effect model is used for low heterogenicity while the random effect model is used for high heterogenicity; thus, in this study, the random effect model was used to combine the articles regarding the treatment of neonatal hypoglycemia. The fixed-effect model was used for studies regarding the prevention of neonatal hypoglycemia (I2 for prehPOD=7.1%, I2 for hypoglycemia=51.6%). The data were analyzed using the STATA 14 software, and $P<0.05$ were considered significant. The meta-regression was used to assess the relationship between the effects of oral dextrose gel on neonatal hypoglycemia with the sample size and the publication year (19-25).

3. Results

Study selection process

At first, 318 articles were found by consulting the above-mentioned databases. A total of 123 duplicate studies were removed by assessing the titles. The abstract of the remaining 195 studies was evaluated and 186 of the remaining articles were removed based on the study exclusion criteria. Finally, the remaining 9 studies entered the quality assessment step, which showed that all 9 studies had high quality; accordingly, they entered the meta-analysis (Figure 1).

Summary of background information of the articles

In the 9 articles with a sample size of 8755 neonates, the mean neonatal weight ranged from 2890 to 3669 g. Of the 9 selected studies, the effects of oral dextrose gel in preventing neonatal hypoglycemia was investigated in 4 studies, and the effect of oral dextrose gel in treating neonatal hypoglycemia was investigated in 5 studies. Three studies reported OR, and 6 studies reported RR regarding the relationship between oral dextrose gel and neonatal hypoglycemia (Table 1). The specifications of the reviewed articles are provided in Table 2.

The dose of oral dextrose gel was 0.5 mL/kg in all studies. Mean maternal age ranged from 29.2 to 33 years, and their BMI ranged from 26.7 to 29. The studies were published between 2013 and 2021 in the United States, Australia, and New Zealand, although the ethnicity of the participants was not limited to these countries (Table 1).

Table 1. Search strategy

Databases	Search Strategy
Scopus	(TITLE-ABS-KEY ("Dextrose gel") AND TITLE-ABS-KEY (hypoglycemia) AND TITLE-ABS-KEY (Infant, Newborn) AND TITLE-ABS-KEY (prevention OR therapy)
Cochrane	Dextrose gel in Title Abstract Keyword AND neonatal OR infant in Title Abstract Keyword AND hypoglycemia in Title Abstract Keyword AND prevention OR treatment in Title Abstract Keyword-in Trials (word variations have been searched)
Web of Science	TOPIC: (Dextrose gel) AND TOPIC: (prevention OR therapy) AND TOPIC: (hypoglycemia) AND TOPIC: (Infant, Newborn)
PubMed	(Dextrose gel [Title/Abstract]) AND (prevention [Title/Abstract] OR therapy [Title/Abstract]) AND (hypoglycemia [Title/Abstract]) AND (Infant, Newborn [Title/Abstract])

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Evaluating the primary outcome

Oral dextrose gel reduced the risk of neonatal hypoglycemia by OR=0.83 (95% CI: 0.75-0.93); thus, oral dextrose gel is significantly effective in preventing neonatal hypoglycemia. However, it did not show significant effects in treating neonatal hypoglycemia (OR=0.78; 95% CI: 0.57-1.07) (Figure 2).

Subgroup analysis

According to Table 3, 61% of the neonates were born through normal vaginal delivery, 16% had low birth weight (below 2500g), 16% had high birth weight (above 4500g), 51% had diabetic mothers, 20% were premature, and 88% were singleton.

Evaluating the mothers' ethnicities revealed that 39% were New Zealand-European, 21% were Maori, 12% were Pacific, and 34% were Asian. Note that the summation of the percentages of the ethnicities passes 100% as some studies did not mention the mother's nationality; moreover, the most common nationalities have been reported in the studies that considered the mother's nationality (Table 3).

Additional analysis

The meta-regression showed no significant relationship between the effects of oral dextrose gel in the prevention of neonatal hypoglycemia and the studies' publication year (P=0.601). Figure 3 shows an acceding trend from 2013 to 2021, however, this relationship is not statistically significant.

In Figure 4, the meta-regression showed no significant relationship between the effects of oral dextrose gel in the prevention of neonatal hypoglycemia and the sample size (P=0.144); that is, the higher sample size was not associated with higher effectiveness of the oral dextrose gel in preventing neonatal hypoglycemia.

According to Figure 5, the meta-regression showed no significant relationship between the effects of oral dextrose gel in treating neonatal hypoglycemia and the studies' publication year (P=0.865).

According to Figure 6, meta-regression showed no significant relationship between the effects of oral dextrose gel in treating neonatal hypoglycemia and the sample size (P=0.770).

4. Discussion

In these 9 selected studies, a total of 8755 neonates were assessed. Oral dextrose gel reduced the risk of neonatal hypoglycemia by OR=0.83 (95% CI: 0.75-0.93); therefore, oral dextrose gel is significantly effective in preventing neonatal hypoglycemia. However, it did not show significant effects in treating neonatal hypoglycemia (OR=0.78; 95% CI: 0.57-1.07). In addition, the meta-regression showed no statistically significant relationship between the effects of oral dextrose gel on neonatal hypoglycemia with the sample size and the publication year.

On the other hand, 61% of the neonates were born through normal vaginal delivery, 16% had low birth weight (below 2500g), 16% had high birth weight (above 4500g), 51% had diabetic mothers, 20% were premature, and 88% were singleton. Evaluation of the mothers' ethnicities showed that the most and least common ethnicities were New Zealand-European (39%) and Pacific (12%), respectively.

In 2018, a clinician survey was conducted on using oral dextrose gel to treat neonatal hypoglycemia in New Zealand (26). Alsweiler JM et al. stated that 251 physicians from 20 territorial health councils participated in the survey, of which 149 physicians (59%) from 15 territorial health councils stated using oral dextrose gel in treating neonatal hypoglycemia. Oral dextrose gel is widely used in New Zealand for neonatal hypoglycemia.

Table 2. Specifications of articles that entered the meta-analysis process

Author, Year of publication	Type of Disease	OR/RR	Type of Study	Country	Number of Neonatal	Number of Girls	Number of Boys	Dosage (mL/kg)	RR	Low	Up	Mother's Age (y)	Mother's BMI	Ethnicity % (New Zealand European)	Ethnicity% (Maori)	Ethnicity% (Pacific)	Ethnicity% (Asian)	Ethnicity% (Other)	Quality of studies by STROBE
Harris, 2017 (19)	Hypoglycaemia	OR	Randomized, double-blind, placebo-controlled trial	New Zealand	227	119	108	0.5	0.52	0.28	0.94	29.6	28.6	51	28	---	---	21	high
Harris, 2016 (15)	Hypoglycaemia	RR	Follow-up of a randomized trial	New Zealand	184	100	84	0.5	1.11	0.75	1.63	29.8	26.7	50	37	---	---	13	high
Harris DL, 2013 (14)	Hypoglycaemia	RR	Randomized, double-blind, placebo-controlled trial	New Zealand	237	131	106	0.5	0.57	0.33	0.98	29.2	27	53	29	---	---	18	high
Plummer EA, 2020 (20)	Hypoglycaemia	OR	Retrospective cohort study	USA	4666	2154	2512	0.5	0.71	0.51	0.99	---	---	---	---	---	---	---	high
Griffith, 2020 (21)	Pre-hPOD	RR	Prospective follow-up of a randomized trial	New Zealand	360	174	186	0.5	0.77	0.5	1.19	33	29	27.8	9.7	15.8	25.3	21	high
Hegarty JE, 2016 (22)	Pre-hPOD	RR	A Randomized controlled dose-finding trial	New Zealand	415	202	213	0.5	0.68	0.47	0.99	32.5	27.6	12.3	16.2	25.2	20	high
Hegarty JE, 2021 (23)	Pre-hPOD	RR	Randomized, double-blind, placebo-controlled trial	New Zealand	415	---	---	0.5	0.7	0.5	1	---	---	---	---	---	---	---	high
Weston, 2017 (24)	Hypoglycaemia	OR	Randomized, double-blind, placebo-controlled trial	New Zealand	102	---	---	0.5	1.3	0.62	2.77	---	---	---	---	---	---	---	high
Harding JE, 2020 (25)	Pre-hPOD	RR	Randomized, double-blind, placebo-controlled trial	New Zealand and Australian	2149	---	---	0.5	0.88	0.8	0.98	32.2	---	24.2	11.3	5.9	50.4	7	high

Table 3. Characteristics of neonatal and maternal

Subgroups	Number (%)	Number of Studies	I2 (%)	P
Vaginal birth	%61 (%58, %65)	3	0%	0.969
Singleton	%88 (%84, %91)	5	86.1%	<0.001
Infant of a mother with diabetes	%51 (%18, %84)	7	99.9%	<0.001
Preterm	%20 (%15, %26)	7	98.2%	<0.001
Small (weight < 2500 g)	%16 (%12, %20)	7	95.5%	<0.001
Large (weight > 4500 g)	%16 (%0, %34)	7	99.9%	<0.001
Ethnicity (New Zealand-European)	39% (28%, 49%)	6	96.9%	<0.001
Ethnicity (Maori)	21% (14%, 27%)	6	95.5%	<0.001
Ethnicity (Pacific)	12% (5%, 20%)	3	96.1%	<0.001
Ethnicity (Asian)	34% (15%, 53%)	3	98.9%	<0.001
Ethnicity (Other)	17% (10%, 23%)	6	95.2%	<0.001

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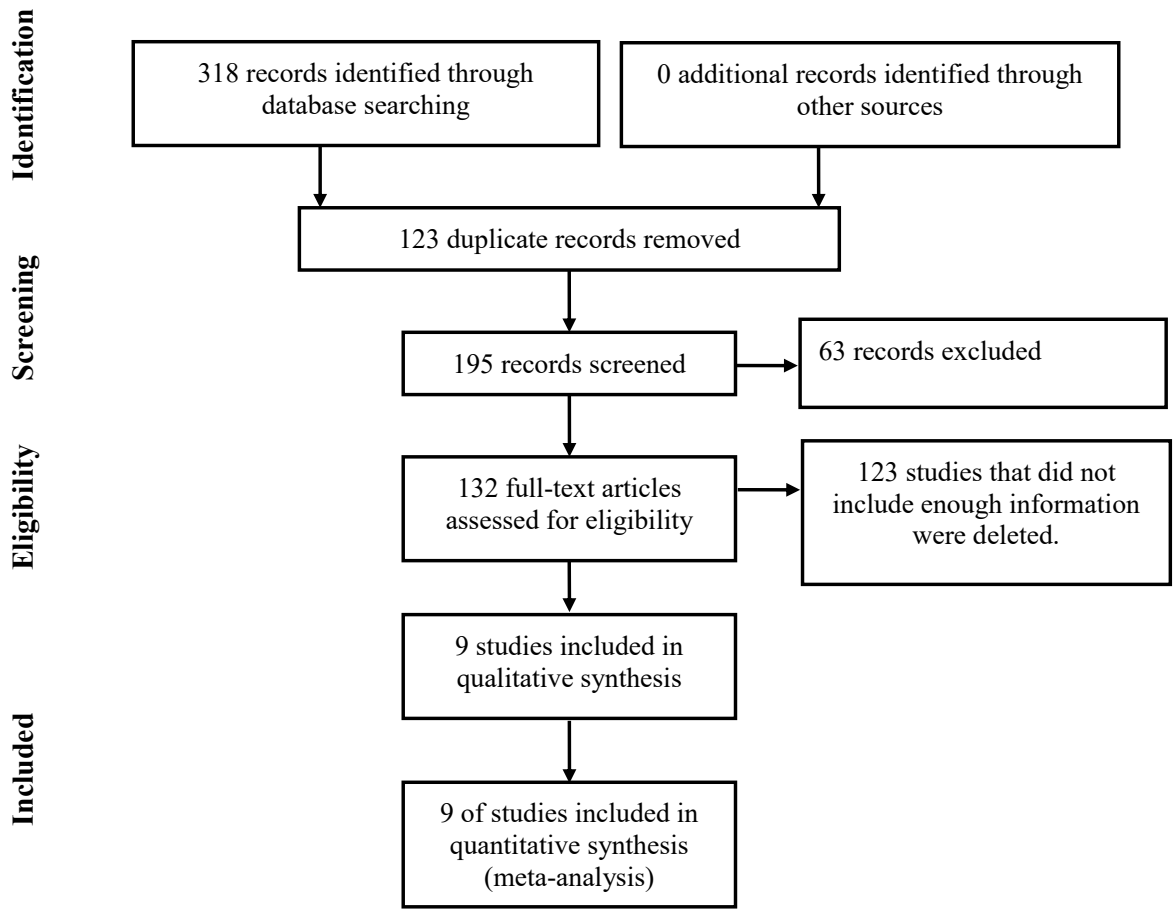

Figure 1. Process of entering the articles into the systematic review and meta-analysis

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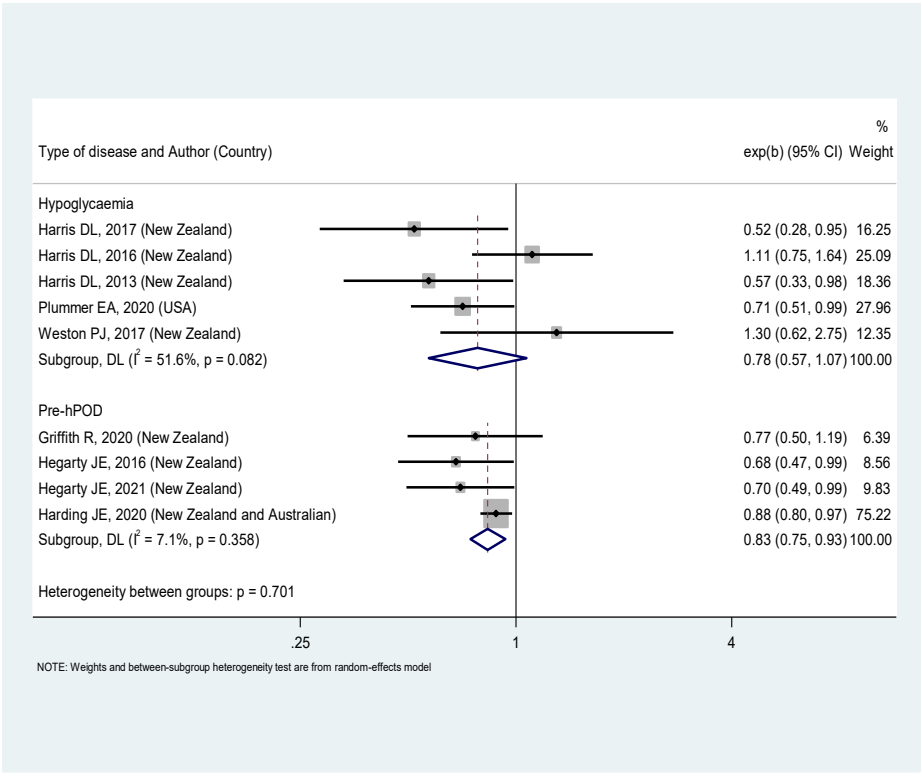

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Figure 2. Effects of oral dextrose gel in preventing and treating of neonatal hypoglycemia based on study year and country

Increased accessibility to dextrose gel and clinical guidelines have probably increased the use of oral dextrose gel (26). This study supports the necessity of the present meta-analysis.

In 2017, Hegarty JE et al. reviewed the effects of oral dextrose gel in preventing neonatal hypoglycemia (27). They conducted a randomized controlled trial on 415 neonates and concluded the statistically significant effects of oral dextrose gel in reducing the risk of neonatal hypoglycemia (RR=0.76; 95% CI: 0.62-0.94) (27). They also stated that this intervention's number needed to treat equaled 8. Edwards T et al. conducted a meta-analysis in 2021 in which they investigated the effects of oral dextrose gel in the prevention of neonatal hypoglycemia (28). They investigated 2 studies and concluded that oral dextrose gel reduces the risk of neonatal hypoglycemia and prevents this disturbance (RR=0.87; 95%

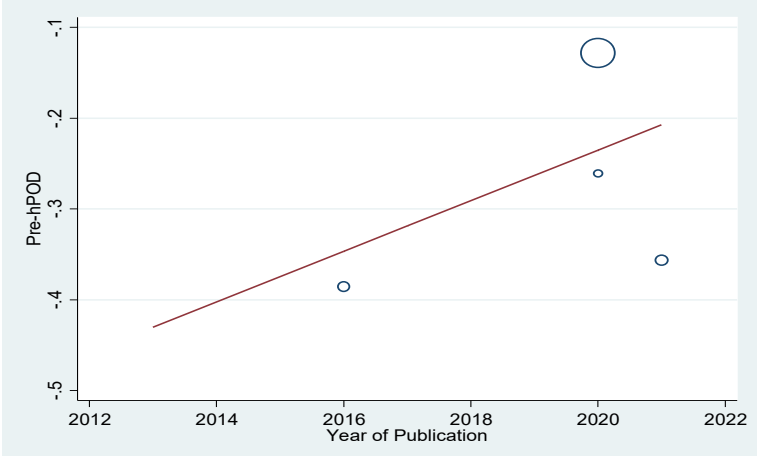

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Figure 3. Meta-regression of the relationship between the effects of oral dextrose gel in preventing neonatal hypoglycemia and studies' publication year

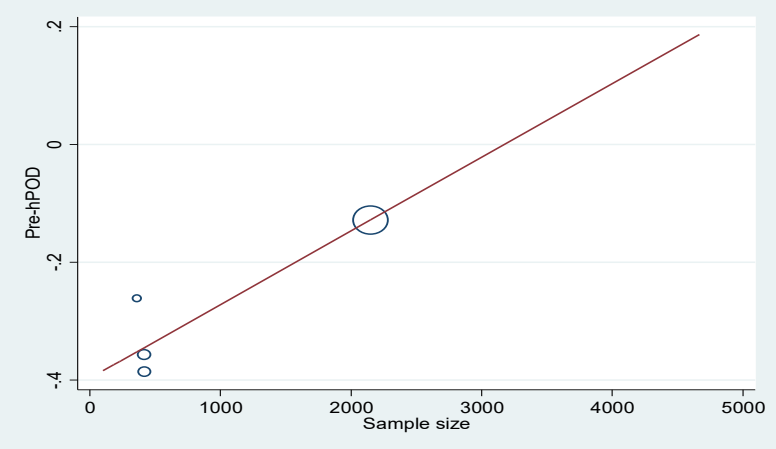

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Figure 4. Meta-regression of the relationship between the effects of oral dextrose gel in preventing neonatal hypoglycemia and the sample size

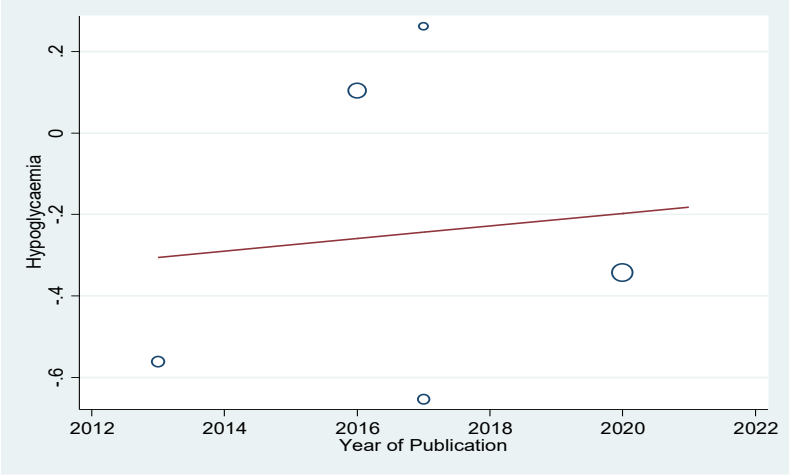

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Figure 5. Meta-regression of the relationship between the effect of oral dextrose gel in treating neonatal hypoglycemia and studies' publication year

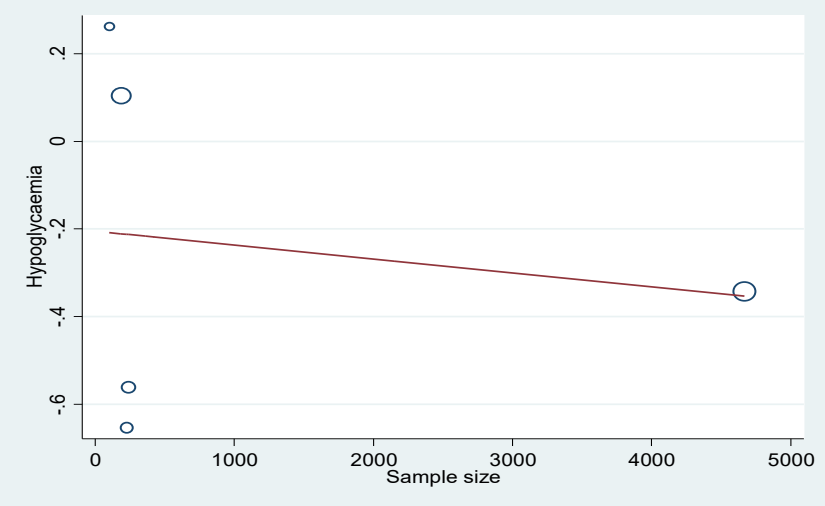

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Figure 6. Meta-regression of the relationship between the effect of oral dextrose gel in treating neonatal hypoglycemia and the sample size

CI: 0.79-0.95) (28). The results of these 2 studies are in line with the present study's findings.

In 2017, Chandrasekharan P et al. reviewed the effects of oral dextrose gel in the treatment of neonatal hypoglycemia (29). They investigated 2 studies and 312 neonates collectively. They found that oral dextrose gel did not reduce the need for intravenous dextrose compared to placebo, however, it reduced mother and neonate separation (29). In 2016, Weston et al. reviewed the effects of oral dextrose gel in treating neonatal hypoglycemia (24). They included 2 randomized controlled trials in their study and concluded that no evidence suggests the difference between dextrose gel and placebo gel on the major sensory neural loss and the need for intravenous dextrose, although the probability of nourishment has increased merely by breastfeeding (24).

The results of these 2 studies are in line with the findings of the present meta-analysis. Accordingly, previous studies have shown the significant positive effects of oral dextrose gel in preventing neonatal hypoglycemia. However, no significant relationship has been observed in treating neonatal hypoglycemia. The findings of the present meta-analysis are reliable as this study is the first and most comprehensive meta-analysis on the effects of oral dextrose gel in preventing and treating neonatal hypoglycemia. Previous review articles investigated a maximum of 415 neonates, while the present meta-analysis included 8755 neonates. On the other hand, previous review articles investigated a maximum of 2 studies, while 9 studies were investigated in the present meta-analysis. Moreover, previous studies investigated the effects of oral dextrose gel in either the prevention or the treatment of neonatal hypoglycemia, while the present study is the first meta-analysis on both prevention and treatment of neonatal hypoleukemia investigating the relationship between oral dextrose gel and neonatal hypoglycemia.

Study limitations

Since 0.5 mL/kg oral dextrose gel was used in all studies, no inferential analysis based on the dose of oral dextrose gel was possible. Since the selected articles did not assess the effects of oral dextrose gel on neonatal hypoglycemia by gender, no gender-specific analysis was possible. Because of the limited number of studies and the non-homogenous distribution of the studies in different countries, country- or continent-specific analysis was not possible. In addition, given the limited number of included studies, we could not prove separate analyses by age group or mean neonatal weight. Thus, no information is available regarding the relationship between oral dextrose gel and neonatal hypoglycemia at different neonatal ages and weights.

5. Conclusion

Oral dextrose gel effectively prevented neonatal hypoglycemia and significantly reduced the risk of neonatal hypoglycemia. However, it did not show statistically significant effects in the treatment of neonatal hypoglycemia. Thus, it is recommended that further clinical studies be conducted in this field. Considering the limited number of published studies in this regard (4 studies on the prevention and 5 studies on the treatment of neonatal hypoglycemia), it is suggested that more studies be performed and published in this regard so that we can make conclusions regarding the effects of oral dextrose gel in preventing and treating neonatal hypoglycemia with higher certainty. Moreover, it is suggested that different doses of oral dextrose gel be used in future studies to overcome the limitations of the present study. Also, it is recommended that similar studies be performed in low- and middle-income countries to avoid limiting results to a few countries. Researchers may conduct future studies on specific groups, such as preterm neonates, neonates of diabetic mothers, and so on, considering the risk factors of neonatal hypoglycemia. Results of the meta-regression showed no statistically significant relationship between the effect of oral dextrose gel on neonatal hypoglycemia with the sample size and the publication year in both prevention and treatment of neonatal hypoglycemia. Thus, it may not be concluded that the effects of oral dextrose gel on neonatal hypoglycemia had an ascending or descending trend.

Ethical Considerations

Compliance with ethical guidelines

Ethical issues (plagiarism, data fabrication, double publication) have been thoroughly observed by the authors.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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