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Original Article (Pages: 6529-6537)

Glucose Oral Solution as A Pain-Relieving Agent In Infantile Colic: A Double Blinded Randomized Clinical Trial

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Abstract

Background

Infantile colic (IC) is a common painful disorder within early months of life. There is no definitive therapeutics for IC. In present study aimed to assess pain-relieving potential of glucose administration in infantile colic.

Materials and Methods

This was a double blinded randomized clinical trial performed during May 2015-June 2017 in pediatric ward of Amir-Al-Momenin Hospital, Zabol city, Iran. Overall, 72 infants were randomly assigned to either glucose or simethicone groups (36 infants per group). Treatments were continued for 28 days with either 25% or 30% glucose solution and 2.5 mg/kg simethicone. Outcomes were assessed at the end of the intervention (28 days). Statistical analysis was done in SPSS version 22.0.

Results

Males and females constituted 20 (55.5%), and 16 (45.5%) in glucose administrated, and 23 (63.8%) and 13 (36.2%, P=0.4) in simethicone group respectively. The mean age (days) was 19.1±3.8 and 20.2±4.9 for glucose and simethicone administrated groups, respectively (P=0.2). The crying times per day significantly reduced in both groups (mean reduction in crying times of 3.7±2.1, and 6.3±2.1 hours in glucose and simethicone groups, respectively). Moreover, 25% and 44.4% of infants in glucose and simethicone groups achieved ≥ 50% reduction in crying time, respectively (P=0.06). According to the glucose dose, infants who received 30% glucose solution significantly revealed higher ratio of ≥ 50% reduction in crying time (47.3%) than those received 25% glucose solution in which no cases fulfilled this outcome (P<0.0001).

Conclusion

Glucose may be a useful candidate to be considered as a pain-relieving agent in infantile colic.

Key Words: Abdominal Cramps, Glucose, Infantile Colic, Simethicone.

*Please cite this article as: Shahramian I, Moradi M, Afshari M, Delaramnasab M, Ebrahimi M, Sargazi A, et al. Glucose Oral Solution as A Pain-Relieving Agent In Infantile Colic: A Double Blinded Randomized Clinical Trial. Int J Pediatr 2017; 5(12):6529-37. DOI: **10.22038/ijp.2017.27284.2353**

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Received date: Sep.28, 2017; Accepted date: Nov.12, 2017

1- INTRODUCTION

Infantile colic (IC) is a common disorder within early months of life. IC has been described as unexplainable excess crying of healthy infants during the three first months of their lives. The frequency of IC has been estimated as 5-25% (1, 2). Nevertheless, as high as 40% of one year old children may experience IC (3). IC is supposed to occur most frequently at 6-8 weeks following birth and resolving spontaneously at 3-4 months of age (1). Regardless of breast or formula feeding, IC infants render acceptable developmental status. Nevertheless, the condition incurs high financial and psychological burden annually due to recurrent physician appointments (4).

IC is a very controversial disease regarding diagnostic and therapeutic parameters. This ambiguity may root in relatively obscure etiology of IC. Some risk factors have been proposed for IC such as lactose intolerance, cow's milk hypersensitivity, deranged gut microbial flora, phycological and neurological irregularities, inappropriate feeding methods, and mother's related factors such as smoking and eating habitants, though the exact mechanism remains elusive (4-6). The most common definition of IC uses time span of crying as the most acceptable diagnostic feature. On a review study of randomized clinical trials on IC, 19 different outcomes have been described. Based on this, IC is diagnosed in a healthy infant with history of crying for three hours per day, three days per week, for a minimum of three weeks.

Not even the definition of IC, but also its therapeutic options have been defined differently by researchers (1). Therapeutic options in infantile colic are limited, and their effectiveness is variable which is mainly due to undetermined etiology. Several efforts have been dedicated to find an effective therapeutic for IC including various nutritious formulas. Role of probiotics has been studied as preventive measures against IC (7-9). As well, pain reducing agents such as simethicone have been extensively tried as managemental strategies in colicky infants (4). Effectiveness of these agents is not established in IC, on the other hand, physicians should be provident in prescription these pharmaceutical agents in very young infants due to their potential side effects. There is no definitive therapeutics for infantile colic, and there are limited studies on the analgesic role of glucose in IC despite proposed pain relieving effects of glucose in neonates. Here, we assessed the pain-relieving potential of glucose administration in neonate with infantile colic.

2- MATERIALS AND METHODS

2-1. Study design and population

This was a double blinded randomized clinical trial performed during May 2015-June 2017. The study was conducted in a single center at Pediatric ward of Amir-Al-Momenin Hospital affiliated with Zabol University of Medical Sciences, South East of Iran. Our study was registered at the Iranian Registry of Clinical Trials (IRCT.2017092636423N1).

2-2. Methods

Thirty-six infants with infantile colic were selected. Sample size was chosen according to a previous similar study to be 72 infants allocated to control and intervention groups (36 infants per group) according to CONSORT guidelines (**Figure.1**) (10). Wessel diagnostic criteria was adapted for including infants into study (i.e; incessant crying $\geq$ 3 hours per day, at least three days per week, and for three weeks, known rule of three) (11). The infants were randomly allocated to either intervention or control groups. Randomization was achieved by creating random sequences of numbers using an online tool (https://www.randomizer.org).

2-3. Measuring tool

Recording of crying times was based on a standard diary form presented by Barr et al. in 1988 (12). This tool has been evaluated and validated by several studies (13, 14). According to this protocol, crying times of babies are documented in four time zones; morning (6 AM-12 AM), afternoon (12 AM- 6 PM), night (6 PM-12 Midnight), and after midnight (12 Midnight- 6 AM). This had been explained to the mothers that only crying episodes that are not clearly related to hunger diaper change, or sleep requirements should be documented. We also explained to the mothers that crying episodes with less than five minutes (which are probably due to above mentioned non-IC causes) are not needed to be documented. A sheet was handed to the mothers for recording the information. Outcomes used for this study were reduction in daily crying duration, ratio of infants who achieved at least 50% reduction in daily crying time, as well as maternal perception of infant's condition on a qualitative scale at the end of the intervention.

2-4. Interventions

The infants in control group received simethicone (Tolidaru Co. Tehran, Iran; 2.5 mg/ Kg); while those assigned to the intervention group were administrated with glucose (either 25% or 30% adjusted for the weight of infants). Either 25% or 30% glucose solutions were prepared by adding 25 ml and 30 ml distilled water to 50% Dextrose (D-glucose polymer) solution (Shaheed Qazi Co., Tabriz, Iran), respectively. The drugs had been fed to the infants by mothers. Treatments continued for 28 days.

2-5. Ethical consideration

The study was in line with Ethics consideration provided by Committee on Publication Ethics, and Helsinki Declaration for medical research. Mothers were interviewed at the entry for obtaining base line characteristics. Parents were requested to fill out an informed consent form before including into the study. The study was approved by Ethical Committee of Research of Zabol University of Medical Sciences (Code: Zbmu.1.REC.1396.95).

2-6. Inclusion and exclusion criteria

We recruited an age spectrum ranging from three weeks to six months as previously described (11). Infants with serious disorders, and history of taking previous medications for infantile colic were not included.

2-7. Data Analyses

Data were entered into statistical software (SPSS 19.0 version). Normality of data was checked by Shapiro Wilk test. Univariate analysis for qualitative variables was executed by Chi-square, and mean differences between groups was checked by student t-test (for normally distributed data) and Mann-Whitney U-test (for non-normally distributed).

3- RESULTS

The aim of present study was to evaluate pain-reliving effects of glucose solution in infants with infantile colic. Seventy-six infants who fulfilled the criteria for diagnosis of IC were randomly allocated to either glucose or simethicone groups using block randomization method. There was no significant difference for base line characteristics of the participants and their mothers in these groups except for high risk delivery in mothers which was higher in mother of infants in simethicone group (65.6%) respective to mothers in glucose group (34.4%) (**Table.1**). Likewise, no significant differences were observed between the two groups regarding infants' age, weight, height, and mothers' delivery age (**Table.2**). In both glucose and simethicone groups, crying times per day was significantly reduced after 28 days of

treatment (mean reduction in crying times of 3.7±2.1, and 6.3±2.1 hours per day for glucose and simethicone groups respectively). Regarding another outcome, 25% of infants in glucose group achieved at least 50% reduction in crying time, while this ratio was 44.4% in simethicone group (**Table.3**). When subcategorizing infants in glucose groups respective to the dose of glucose (25% or 30%), infants who received higher dose significantly revealed higher ratio of ≥50% reduction in crying time (47.3% in 30% glucose with no infant in 25% glucose achieved this outcome (**Table.4**).

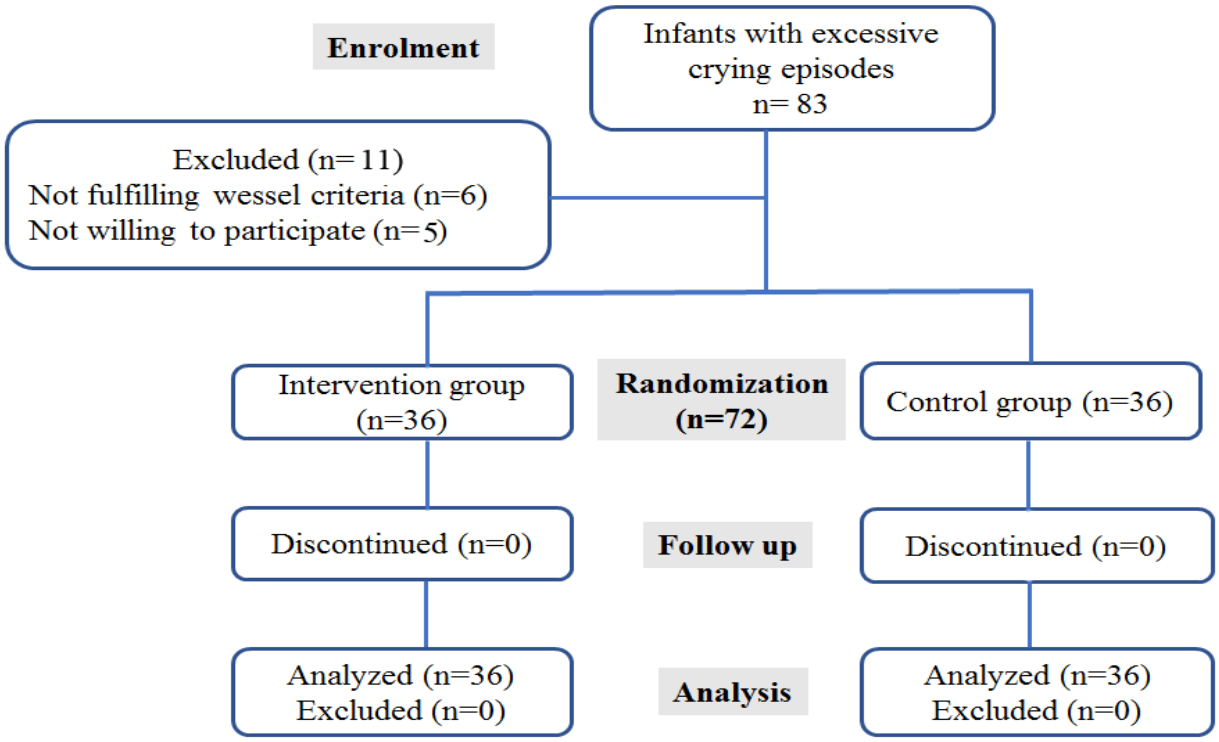

Fig.1: CONSORT flow-diagram of the study process. Number of neonates in each phase; enrolment, randomization, follow up and analysis has been indicated.

Table-1: Features of infants and their mothers in two experimental groups; glucose or simethicone received.

Base line characteristics		Total	Glucose n=36 Number (%)	Simethicone n=36 Number (%)	*P-value
Gender	Male	43 (59.7)	20 (46.5)	23 (53.5)	0.4
	Female	29 (40.3)	16 (55.2)	13 (44.8)	
Mother's education	Illiterate	28 (38.9)	14 (50)	14 (50)	0.3
	Elementary	17 (23.6)	6 (35.3)	11 (64.7)	
	Pre-high school	15 (20.8)	10 (66.7)	5 (33.3)	
	High school	12 (16.7)	6 (50)	6 (50)	
	Academic	0 (0)	0 (0)	0 (0)	
Father's job	Unemployed	0 (0)	0 (0)	0 (0)	0.4
	Farmer	19 (26.4)	7 (36.8)	12 (63.2)	
	Worker	17 (23.6)	8 (47.1)	9 (52.9)	

	Government employee	6 (8.3)	3 (50)	3 (50)	
	Self-employment	30 (41.7)	18 (60)	12 (40)	
Mother's job	Housewife	68 (94.4)	33 (48.5)	35 (51.5)	0.3
	Government employee	0 (0)	0 (0)	0 (0)	
	Self-employment	4 (5.6)	3 (75)	1 (25)	
Number of children in the family	One	3 (4.2)	2 (66.7)	1 (33.3)	0.3
	Two	12 (16.7)	5 (41.7)	7 (58.3)	
	Three	23 (31.9)	10 (43.5)	13 (56.5)	
	Four	19 (26.4)	8 (42.1)	11 (57.9)	
	Five	9 (12.5)	6 (66.7)	3 (33.3)	
	Six	6 (8.3)	5 (83.3)	1 (16.7)	
Term Condition	Term	69 (95.8)	34 (49.3)	35 (50.7)	0.5
	Pre-term	3 (4.2)	2 (66.7)	1 (33.3)	
Nausea and vomiting at delivery	Yes	39 (54.2)	19 (48.7)	20 (51.3)	0.8
	No	33 (45.8)	17 (51.5)	16 (48.5)	
Type of delivery	Vaginal	55 (76.4)	30 (54.5)	25 (45.5)	0.1
	Cesarean	17 (23.6)	6 (35.3)	11 (64.7)	
High risk delivery in mother	Yes	32 (44.4)	11 (34.4)	21 (65.6)	0.01
	No	40 (55.6)	25 (62.5)	15 (37.5)	
Infant nutrition	Breast-fed	58 (80.6)	33 (56.9)	25 (43.1)	0.2
	Formula-fed	8 (11.1)	1 (12.5)	7 (87.5)	
	Breast/formula-fed	6 (8.3)	2 (33.3)	4 (66.7)	
Previous children with infantile colic	Yes	28 (38.9)	12 (42.9)	16 (57.1)	0.3
	No	44 (61.1)	24 (54.5)	20 (45.5)	
History of smoking in mother	Yes	0 (0)	0 (0)	0 (0)	-
	No	72 (100)	36 (50)	36 (50)	
History of GI disorders in mother	Yes	14 (19.4)	5 (35.7)	9 (64.3)	0.2
	No	58 (80.6)	31 (53.4)	27 (46.6)	
Family history of allergic diseases	Yes	3 (4.2)	1 (33.3)	2 (66.7)	0.5
	No	69 (95.8)	35 (50.7)	34 (49.3)	
History of cow's milk consumption in mother	Yes	70 (97.2)	34 (48.6)	36 (51.4)	0.1
	No	2 (2.8)	2 (100)	0 (0)	
History of cow's milk consumption by Infants	Yes	0 (0)	0 (0)	0 (0)	-
	No	72 (100)	36 (50)	36 (50)	
*; Chi-square test					

Table-2: A comparison of infants' age, weight, and height between infants in glucose and simethicone groups.

Parameters	Glucose	Simethicone	P- value
Age (days)	19.1 ± 3.8	20.2 ± 4.9	0.2 *
Weight at birth (grams)	3241± 376.6	3210 ± 274.4	0.6
Height (centimeter)	50.7±0.7	50.9 ± 0.4	0.1 *
Weight at present (grams)	3726±459.1	3776.9±291.3	0.5
Age of mother at delivery (years)	35.2±4.6	34.5±5.2	0.5
*; Mann-Whitney U test.			

Table-3: Outcome of infantile colic between either glucose or simethicone fed colicky infants.

Infantile colic outcomes		Glucose n=36	Simethicone n=36	Between group analysis P-value
Crying time before intervention (hours per day)		13.1±2.7	15.4±3.6	0.1
Crying time after intervention (hours per day)		9.4±2.8	9.1±3	0.6
Within group analysis P- value		<0.0001	<0.0001	
Mother's assessment of infant condition	Much Better	21 (58.3 %)	15 (41.7%)	0.1
	Better	15 (41.7%)	21 (58.3 %)	
Mean reduction in crying time		3.7±2.1	6.3±2.1	<0.0001
Reduction of crying time ≥ 50%		9 (25%)	16 (44.4%)	0.06*
*; Fischer exact test.				

Table-4: A comparison of infantile colic outcomes between colicky infants who received 25% or 30% glucose solution.

Infantile colic outcomes		Glucose Dose=2 mg/kg (25%), n=17	Glucose Dose =2.5 mg/kg (30%) n=19	Between group analysis P- value
Crying time before (hours per day)		14.3±3.2	12.1±1.6	0.4
Crying time after (hours per day)		10.7±2.1	8.2±2.9	0.008
Within group analysis P value		<0.0001	<0.0001	
Mother's assessment of infant condition	Much Better	7 (41.1%)	14 (73.6%)	0.05*
	Better	10 (58.9%)	5 (26.4%)	
Mean reduction in crying time		3.6±2.2	3.9±2.1	0.7
Reduction of crying time ≥50%		0 (0)	9 (47.3%)	0.003
*; Fischer exact test.				

4- DISCUSSION

In current study, pain relieving effects of glucose was assessed in colicky infants. After 28 days of administration, glucose reduced mean crying times per day for 3.7±2.1 hour. In control group who received simethicone, the reduction time reached 6.3±2.1 hours per day. Moreover, 25% of infants in glucose group achieved at least 50% reduction in crying time, while this ratio was 44.4% in simethicone group. Infants who received 30% glucose solution significantly revealed higher ratio of ≥50% reduction in crying time (47.3%) than those received 25% glucose solution in which no cases fulfilled this outcome (P<0.0001). Infantile colic occurs most commonly within the second month of life (5). Some suggested etiologic factors have been noted for IC such as abdominal distention, dietary allergies such as lactose intolerance, and gas production, however, the precise etiology is not well understood. Phenotypically, IC may be identified with gastrointestinal problems such as altered integrity of feces, restlessness and regurgitation. These, if present, will be accompanied by incessant non-relievable crying. Outcomes considered in clinical trials for IC have been variables. The most common outcomes used in researches are ≥ 50% reduction in average crying time and mean average daily crying time (1, 2, 14-16). Parenteral judgment has also been used by 10% of RCTs on IC (1). We used all the three outcomes (i.e. ≥ 50% reduction in crying time, mean crying duration, and maternal judgment) in present study. We found that administration of glucose for infants with IC for 28 days reduced ≥ 50% average

crying time of colicky infants in 25% of cases. However, with those who received higher dose of glucose (30%), average ≥ 50% reduction of crying time was observed in 47% of cases. Regarding mean duration of daily crying time, infants who received glucose revealed a mean reduction of 3.7±2.1 hours, which was lower in comparison to those administrated with simethicone (6.3±2.1 hours daily). There were scare studies evaluating the effectiveness of glucose in management of IC (1). Glucose solution with 30% concentration was shown to be effective in treating IC in 64% of infants who take the solution for four days, with 20% of them achieving marked improvements (18).

In another study, Duygu et al. found sucrose solution as an effective intervention for improving IC signs (19). Pain resolving features of 30% oral glucose has been described in non-IC conditions in neonates previously (10, 20, 21). Pharmacological agents in used for IC such as Dicyclomine hydrochloride and Cimetropium bromide have disadvantages of possible side effects in pediatrics (22). Although safety of long term usage of sweet solutions has been debated in neonates (23), glucose as it is a readily available and inexpensive therapeutic with acceptable short-term safety profile.

Majority of previous clinical trials in IC has been conducted on probiotics which are alive and beneficial microbes for human physiology when digested. Beneficial effects on *Lactobacillus Reuteri* on IC have been previously shown as reduction in average crying times (11, 16, 24). In a study assessing *L. Reuteri* DSM 17938 effects on IC, 17% of infants in probiotic group achieved at least 50% reduction in crying duration on three weeks (11), which is comparable with the rate we observed for glucose administrated infants in our study. Controversies on effectiveness of probiotics raised with publication of a recent clinical trial that suggested no role for L. Reuteri at one, two, and three weeks following administration (25). On the other hand, infants treated with a symbiotic regime comprising Lactobacillus, Streptococcus, and Bifidobacterium bacterial strains, as well as fructooligosaccharide (fructo-oligosaccharide) for one month showed 50% reduction in average crying time in 87% of the infants (17). In another clinical trial study, fermented galacto/fructo-oligosaccharide were used as preventive measures for IC, and the results indicated effectiveness of fermented formulated diet on both incidence and daily crying time (26). These observations may indicate a synergistic effect between carbohydrates and probiotics in attenuating painful sequala in colicky infants. However, this need to be more studied in future.

Previous clinical trials on IC suffers from a number of methodology flaws including non-blinded trials (24), or un even distribution of baseline characteristics (16). Potential cofounding effects of demographic and maternal factors in clinical trial studies on IC may be in part responsible for inconsistent results (27). Maternal diet may be a factor influencing occurrence of IC, as mothers who consumed higher contents of proteins and potato were more likely to had babies with IC (28). Substantial role of cow milk and its derived formula has been proposed as an etiologic factor for IC. In a study by Kheirkhah et al., proportion of infants fed with formula was significantly higher (23%) in IC group that non-IC (2%) (29).

In the study of Savino et al., it was revealed that infants with colic had lower total enumerated of bacteria in their feces, while the ratio of coliform organisms was significantly higher in infants with colic respective to those without colic (30). One of the benefits of our study was effective randomization which rendered fairly comparable baseline features of infants and their mothers in glucose and

simethicone groups. In particular, only 14 infants in our experiment were formula fed (8, 11.1%) or mixed breast and formula-fed (6, 8.3%). In infants who were administrated with glucose, only 1 infant had been formula fed, while two had been mixed breast/formula fed. Considering this, if the type of nutrition in infants could potentially modulate glucose effectiveness was not applicable for us to scrutinize. Therefore, our results are more generalizable to breast fed infants.

5- CONCLUSION

Glucose, as an analgesic agent, reduced average crying time by 50% and mean crying time in a considerable ratio of colicky infants in our study. Regarding great safety profile of glucose, it is recommended to consider this agent as a complementary non-pharmaceutical intervention for infantile colic.

6- AUTHOR CONTRIBUTIONS

Iraj Shahramian contributed in concept and design, revising manuscript. Mandana Moradi and , Mahdi Afshari conducted data collection and analysis, Mojtaba Delaramnasab contributed in study design and preparing the manuscript, Mahvash Ebrahimi and Alireza Sargazi participated in data collection, and Ali Bazi contributed in study design and drafting the manuscript.

7- CONFLICT OF INTEREST

Authors have no conflict of interests. The study was approved by the Ethical Committee of Zabol University of Medical Science (Code: Zbmu.1.REC.1396.95).

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