Efficacy of Oral Glucose in Reducing Behavioural Responses to a Noxious Stimulus in Healthy Term Neonates

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Abstract

The aim of the study is to evaluate the effect of orally administered glucose, at concentrations of 5% and 30%, on the nociceptive behavioural pain response among full-term neonates who underwent the heel puncture technique. This is a prospective, randomized, double-blind, placebo-controlled trial which was registered at clinicaltrials.gov under the number Makassed General Hospital Protocol Record 1722017 in July 2017. This trial studied the effect of glucose solution on pain relief in 244 full-term healthy neonates who underwent a heel prick procedure. Neonatal pain was assessed using the Neonatal Infant Pain Scale (NIPS) and the duration of cry. The results showed that neonates receiving 30% glucose during the procedure had significantly the lowest mean NIPS (mean=4.89) compared to placebo and 5% group (mean=5.8 and 5.2 respectively) (p=0.03). Neonates in the glucose groups of both 5% (65.9%) and 30% (70.4%) scored significantly as having less pain compared with the placebo group (86.4%) (p=0.01). The neonates in the 30% glucose group cried less and had a significantly shorter crying duration (mean: 39.9 seconds) than in the 5% and placebo groups (p=0.04).

Conclusion: 30% glucose and, to a lesser extent, 5% glucose were effective in reducing the behavioral pain response from heel prick procedures in term neonates.

What Is Known

- Oral glucose, in different concentrations, is still debatable regarding its efficacy in pain relief among neonates

What is New:

- Glucose with 30% concentration and, to a lesser extent, glucose with 5% concentrations were effective in reducing the behavioral pain response from heel prick procedures in term neonates.

Introduction

According to animal models and human studies, the pain system in neonates is not mature [1]. However, studies have shown that neonates have structures to receive nociceptive information and transmit them to higher centers, a condition necessary for pain perception, but not necessarily sufficient [2, 3]. Verriotis *et al.* stated that the peripheral input of nociceptive information can reach the somatosensory cortex starting from 28 to 30 weeks of gestation, and the development of the brain capabilities for information integration occurs between 37 and 40 weeks of gestation [1]. Neonates often display variations in physiological and behavioral reactions to a noxious stimulus; thus, these variations are often used to assess pain in this population [4]. The use of behavioral observations to measure pain have been questioned by the fact that brain activity is not always in line with behavioral responses [5]. The assessment of pain in neonates is challenging, thus, the health professional may rely on the behavioral and physiological reactions to noxious stimulus for pain assessment in neonates [6]. Neonates present in

the neonatal intensive care unit (NICU) are exposed to up to 150 painful procedures daily and they systematically receive analgesics [7, 8]. Healthy neonates who remain in the maternity wards seldom receive analgesics for painful procedures [6], which mostly include sampling of blood for bilirubin measurement or metabolic screening [9]. Unalleviated pain can cause significant neonatal distress, and may have long-term consequences [10]. For these reasons, it is always recommended to alleviate pain when feasible [11]. There is a large variety of pharmacological and non-pharmacological intervention for pain management that can be used during painful procedures in neonates. Pharmacological agents are generally not used to relieve pain in neonates due to their adverse effects [12]. The use of non-pharmacological measures, such as skin-to-skin care of the mother, breastfeeding, non-nutritive suction, facilitated tucking and wrapping, and administration of sweet solutions for pain alleviation in neonates, has gained more interest in the recent years [13, 14]. These techniques are inexpensive, available, easy, and effective to reduce pain during painful procedures.

The effect of oral administration of sweet solutions has been studied often and has been shown to be an effective to prevent and manage pain and stress in the neonates [15, 16]. A Cochrane review showed that sweet solutions, namely glucose, reduces pain scores and crying during single heel lances and venipunctures in both term and preterm neonates [17]. Sucrose, in specific, has been studied more frequently than glucose, and have become a popular solution in recent years to relieve minor pain in neonates [18, 19, 20, 21]. However, as sucrose is not available in the neonatal nursery, it is not used routinely in neonatal care [16]. Glucose, however, is widely used intravenously in the neonatal care unit, but studies on the analgesic effect of glucose in neonatal pain are very limited [17]. If the antinociceptive effect of glucose is effective, it may be preferable due to its availability and accessibility. Therefore, it is essential to establish an evidence base for glucose in the management of neonatal pain.

The maximum analgesic effect can be perceived 2 minutes after administration of sweet solution and can last approximately 10 minutes [18, 19, 20].However, the most effective dose and glucose concentration for painful procedures remains uncertain for routine practice [22]. The influence of the volume and the concentration of the sweet solution on the analgesic effect is still unclear. The dose of 2 ml of oral glucose was chosen in most studies, especially in term neonates, but other studies have already stated an effect with 0.05 ml [23].

Objectives

The aim of this study is to evaluate the effect of orally administered glucose, at concentrations of 5% and 30%, on the behavioral response to a noxious stimulus among full-term neonates who underwent the heel puncture technique and the safety of method of its oral administration.

Materials And Methods

Study design

This study was a prospective, randomized, double-blind, placebo-controlled study of healthy full-term newborns delivered by normal vaginal delivery, undergoing a heel prick test from May 1, 2017, to June 30, 2018. It was conducted at Makassed General Hospital, Beirut, Lebanon, Bekaa Hospital and Chtoura Hospital, Bekaa, Lebanon, in the normal newborn nursery. These hospitals are affiliated with the Faculty of Medicine at Beirut Arab University.

Study Subjects and Data collection

All neonates delivered at Makassed General Hospital, Bekaa Hospital, and Chtoura Hospital and admitted to the normal newborn nursery with criteria presented in Supplementary Table I.

The newborns were randomly allocated to one of three groups: two experimental and one control using sealed envelopes as follow:

Group 1: Control (placebo) group, which included 81 neonates who received 2 ml of sterile water before heel prick.

Group 2: Test group, which included 82 neonates who received 2 ml of 5% glucose before heel prick.

Group 3: Test group, which included 81 neonates who received 2 ml of 30% glucose before heel prick.

All 3 studied groups were matched with respect to all assessed demographic and clinical characteristics. Glucose solutions used in the study were the same used for IV. Dextrose 5% injection USP bags manufactured by serum products and glucose 30% PROAMP injectable solution ampoules were used. The oral solution was warmed to 37°C and was administered slowly over a period of 30 seconds. Heel pricks were performed on the neonates in a warm quiet newborn nursery using Autolet (QuickHeel Lancet), a mechanical device for sampling from the capillaries.

Each set of sequential procedures, including randomization and sampling, was carried out by a team of two pediatricians and three nurses: The first Pediatrician performed the randomization; the second Pediatrician performed the oral administration and the assessment of pain; and one of the three nurses performed in turn the blood sampling.

The following variables were collected: age in hours, gestational age, gender, maternal gravidity, epidural anesthesia during delivery, nationality, Apgar at 1 min and 5 min respectively, type of nutrition (breastfeeding, bottle feeding or combined), circumcision performed prior to enrollment once indicated. The weight in kg and length in cm were also measured at birth for each enrolled newborn. The information was filled in a Clinical Research Form (CRF).

Assessment tools

A combination of behavioral and physiological parameters was utilized to measure each newborn's responses to the heel prick. The behavioural pain indicators were measured using the Neonatal Infant Pain Scale (NIPS), recorded 5 min before and immediately after the procedure, and the presence and the

duration of crying. The state of arousal of each neonate was assessed before heel prick as per Prechtl and Beintema behaviral state/wakefulness [24]. Pain response was assessed by recording the presence of cry, the duration of crying and NIPS.

Sample Size

The primary outcome was the effect of oral glucose on NIPS. We considered that 20% difference in pain score among the three groups with the standard deviation of the NIPS change to be two, with 80% power to detect a one-unit decrease in the NIPS, at the 5% level of error. The sample size for each group was calculated at 63. Taking into consideration 10% drop out, the sample size in each group should be 70.

Statistical Methods

Data entry and analysis was conducted using the Statistical Package for Social Sciences (SPSS, version 24). Categorical variables were presented as number and percent, whereas continuous variables were presented as mean and standard deviation. Bivariate analysis was carried out by using the Chi square for comparing categorical variables, whereas continuous ones were compared using the Student's t-test. Post Hoc test was used to calculate the least significant difference. A multivariate analysis was conducted to control for confounding variables by using the enter method. A *p*-value of <0.05 was used to indicate statistical significance.

Ethical considerations.

The institutional review board at the Makassed general hospital, Chtoura hospital, and Bekaa hospital approved this study. The study protocol was registered at clinicaltrials.gov under the no. Makassed General Hospital Protocol Record 1722017. All parents received an explanation of the study before participation and the parents for voluntary participation signed an informed written consent. Once parents have approved they were asked to sign two informed consents: one copy to remain with them and one for the investigator.

Results

In this multicenter prospective, randomized, double-blind, placebo-controlled study, a total of 260 full-term neonates, delivered by normal vaginal delivery and met the inclusion criteria, were assessed for eligibility in the study and 244 neonates were enrolled. The enrolled neonates were randomly divided into three groups as shown in f**igure 1.** Each group of neonates underwent heel pricks for collection of blood samples for neonatal screening. Baseline characteristics for the study population are presented in **table 1**. There was no significant difference among the placebo, 5% glucose and 30% glucose groups regarding age, gestational age, gender, and epidural anesthesia, Apgar score at 1 and 5 minutes, birth weight, birth length and circumcision.

Within the 30% glucose group, 17.3% (14) of neonates did not cry compared to 6.2% (5) neonates in the 5% glucose group and 7.3% (6) neonates in the placebo group (p=0.04) (**Table 2**). The difference was significant when comparing placebo and 5% glucose groups to 30% glucose group (p=0.024 and 0.044 respectively) (**Table 3**).

When testing the mean duration of cry among the 3 groups, it was the lowest in 30% glucose group and the highest in both 5% glucose and placebo groups (p=0.04) (**Table 2**). This difference was significantly observed when comparing placebo and 5% glucose groups to 30% glucose group (p=0.035 and 0.023 respectively) (**Table 3**).

There was no difference in the mean NIPS among the 3 studied groups before the heel prick procedure (p=0.53). However, neonates in 30% glucose group had the lowest mean NIPS during heel prick procedure when compared to both placebo and 5% glucose groups (p=0.03) (**Table 2**). The difference in the mean NIPS during the procedure was significant only when comparing placebo to 30% glucose group (p=0.009) (**Table 3**).

The mean change in the NIPS before and during the heel prick procedure was significantly the lowest in the 30% glucose group when compared to placebo (p=0.01) (**Table 2**).

During the heel prick procedure, 86.4% (70) of neonates in the placebo group felt pain compared to 65.9% (54) of neonates in 5% glucose group and 70.4% (57) of neonates in 30% glucose group (p=0.01) (**Table 3**). This difference was statistically significant when comparing placebo group to 5% and 30% glucose groups as shown in table 19 (p=0.003 and 0.021 respectively).

Multivariate analysis, using the enter method, was performed to control for factors affecting pain during heel prick procedure. It showed that 5% glucose reduced pain by 25% (OR (95% CI):0.25 (0.11 - 0.57), p=0.001), and that 30% glucose reduced pain by 34% (OR (95% CI): 0.34 (0.14 - 0.79), p=0.01) if either were given to neonates prior to heel prick procedure. However, there was no statistical significance of maternal gravidity, gender, nationality, birth weight, length, Apgar at 1 and 5 min, maternal anesthesia, type of nutrition, duration of the last feed and circumcision on pain in the studied neonates (**Table 4**).

None of the enrolled neonates in the 3 studied groups developed side effects including chocking during oral administration or feet hematoma or hyperglycemia or after the heel prick procedure.

Discussion

Many evidence suggests that the newborn brain may become ready to express noxious stimuli at birth. Novel electrophysiological and haemodynamic studies of nociceptive activity in the human infant brain show that it can process noxious stimulation [1].

Our results demonstrated that 2 ml of glucose 30% and to a lesser extent glucose 5% reduced immediate behavioral parameters and crying caused by acute pain. However, glucose solution did not have an effect

on heart rate, respiratory rate, and SaO_2. However, 30% glucose solution significantly reduced NIPS score compared to both 5% glucose and placebo. Both 5% and 30% glucose were highly effective in reducing pain by 25% and 35% respectively among the neonates. In addition, the percentage of neonates who did not develop crying during the heel prick procedure was significantly higher among the 30% glucose group. Also, the cry duration was the lowest among the 30% group.

Similar to our results, several studies have shown the efficacy of 30% glucose on pain alleviation among neonates undergoing painful procedures [23, [25], [26]]. In addition, a meta-analysis showed that 20% to 30% glucose solutions reduced pain scores and decreased the duration of crying during heel prick and venipuncture compared with placebo (water) or no intervention concluding that. glucose could be an alternative to sucrose solutions in pain alleviation in neonates although still there are no recommendations about the dose or timing of glucose administration [17].

Also, the intense sweetness of the sweet solution increases its effectiveness. It had been demonstrated that concentrations of sucrose more than 12% [25] and concentrations of glucose of more than 10% are effective [[27]]. That is why 30% glucose or 25% sucrose concentrations have been studied in clinical trials. However, these sweet solution concentrations might have side effects including respiratory distress and choking in neonates more than lower concentrations. Based on this, lower concentrations of sweet solutions are preferable to be used in the reduction of pain response in neonates. This trial demonstrated that 5% glucose had reduced pain among full-term neonates undergoing heel prick procedure by 25%, which is in accordance with the results of a previous study, done by Uzelli *et al.* that showed the effectiveness of the same concentration of glucose in pain reduction among preterm neonates during intramuscular injection procedure [26].

Thus in this study, the effect of two glucose concentrations (5% and 30%) on physiologic and behavioral parameters were compared in between and with a placebo group which was sterile water. It is worthy to notify that there are no national guidelines in Lebanon to use pain alleviating measures prior to heel prick procedure in neonates. Second, many published studies included placebo as a control group when studying the analgesic effect of oral sweet solutions on the painful procedures in neonates. This was shown by the meta-analysis performed by Harrison *et al*. which demonstrated that 88% of the published trials, evaluating sweet solutions for analgesia in neonates, included placebo/no treatment arms [[28]].

A higher volume of glucose was used (2 ml) in this study, and the effect of oral sweet solution volume on their analgesic effect is still not clear. Although an optimal dose of both glucose and sucrose has not been determined, an oral dose of 0.1 to 1 mL of 24% sucrose (or 0.2–0.5 mL/kg) 2 minutes before a painful procedure has been recommended, taking into account gestational age, severity of illness, and procedure to be performed [16]. It has been reported that glucose solutions have effects for 2 ml volume [6]. One study demonstrated the effectiveness of 1 ml glucose solution [[29]], but it was shown to be ineffective in another study [[30]]. Increasing the volume of sweet oral solution can prolong the duration of its sweet stimulus. Thus, repeated doses of 0.05 mL sucrose 24% [[31]] or 1 mL glucose 30% [[32]] were found to be more efficacious than a single dose.

The mechanism of action of oral sweet solutions for alleviating the physiologic and behavioural responses to noxious stimulus is still not yet fully identified. It has been proposed that two mechanisms are apparently involved. Firstly, the taste is stimulated by the sweet flavor sensation and this activates the pleasure cortical areas that promote physiological and sensory effects leading to the release of endogenous opioids that act on their own receptors (mainly μ receptors), and this possibly occurs through the dopamine or acetylcholine pathways and thus modulating the painful response. The second mechanism is modulating neuronal transmission of painful stimulus through the action of endogenous opioids on nociceptors [33]. Bembich *et al.* showed in a 2018 study that oral glucose administration, either alone or associated with maternal holding, may block or weaken the processing of cortical pain [34].

This study showed that 30 % glucose provided the most effective reduction of pain during heel prick procedure. When the administered solutions were corrected for possible confounders including male circumcision, the pain-reducing effect remained significant for both 5% and 30% glucose groups.

Strengths And Limitations

The major strengths of this study are being a double-blind randomized clinical trial, its large sample size with comparable basic characteristics among groups and from two different health centers, using the automatic heel lance and using a validated pain assessment. Moreover, crying and its duration was studied as a reliable tool to assess pain, as it was studied in full-term healthy newborns. However, the composite pain scores encompassing behavioral and physiologic items cannot recognize the discordant effects of sweet oral solutions on behavioral and physiologic reactions to blood sampling because they are calculated as the sum of behavioral and physiologic reactions. To overcome the above, we studied the physiologic parameters. With this study design, it was possible to demonstrate that pain therapy with oral glucose solution accentuated the discordance between behavioral and physiologic reactivity by attenuating the behavioral response but leaving the physiologic response unchanged.

Conclusion

2 ml of 30% glucose solution, and to a lesser extent 2 ml of 5% glucose reduced the behavioural response to a noxious stimulus induced by pain in term neonates. Thus, this study supports the use of oral glucose in its two concentration 5% and 30% for immediate pain relief in full-term neonates undergoing heel prick punctures for blood withdrawal. Oral administration of glucose is a safe, inexpensive, and efficient pain-reducing solution that is always available in the hospital ward. By administering the proper glucose solution at the right time, the newborn caregiver can provide effective pain reduction.

Abbreviations

NIPS: Neonatal Infant Pain Scale

Declarations

Funding: “No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article”.

Conflict of interest /Competing interests:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Ethics approval: The institutional review board at the Makassed general hospital, Chtoura hospital, and Bekaa hospital approved this study. The study protocol was registered at clinicaltrials.gov under the no. Makassed General Hospital Protocol Record 1722017.

Consent to participate: All parents received an explanation of the study before participation and the parents for voluntary participation signed an informed written consent. Once parents have approved they were asked to sign two informed consents: one copy to remain with them and one for the investigator.
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Code availability: NA

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Tables

Table 1. Basic Characteristics of the Study Population

Characteristics		Group 1 Placebo (n=81)	Group 2 5% Glucose (n=82)	Group 3 30% Glucose (n=81)	P-value
Age (hours)					
Mean (±SD)		22.16 ± 11.03	22.79 ± 10.81	26.63 ± 15.93	0.06
Gestational age					
Mean (±SD)		38.93 ± 1.05	39.07 ± 0.98	38.85 ± 1.05	0.37
Gender (%)	Male	40 (49.4)	39 (47.6)	42 (51.9)	0.86
	Female	41 (50.6)	43 (52.4)	39 (48.1)	
Epidural anesthesia(%)	Yes	29 (35.8)	38 (53.7)	36 (44.4)	0.35
	No	52 (64.2)	44 (53.7)	45 (55.6)	
Apgar at 1 minute					
Mean (±SD)		8.83 ± 0.44	8.92 ± 0.28	8.86 ± 0.41	0.35
Apgar at 5 minutes					
Mean (±SD)		9.86 ± 0.41	9.98 ± 0.15	9.90 ± 0.30	0.06
Birth weight (Kg)					
Mean (±SD)		3.14 ± 0.38	3.16 ± 0.35	3.22 ± 0.43	0.41
Birth length (cm)					
Mean (±SD)		48.00 ± 1.84	48.00 ± 1.69	48.08 ± 1.74	0.95
Circumcision(%)	No	22 (27.2)	21 (25.6)	21 (25.9)	0.97
	Yes	18 (22.2)	18 (22.0)	21 (25.9)	
	Not applicable	41 (50.6)	43 (52.4)	39 (48.1)	

Table 2. Cry and Pain Score (NIPS) among the Study Population after Heel Prick

Cry (sec)		Group 1 Placebo (n=81)	Group 2 5% Glucose (n=82)	Group 3 30% Glucose (n=81)	P-value
Cry (%)	No	5 (6.2%)	6 (7.3%)	14 (17.3%)	0.04
	Yes	76 (93.8%)	76 (92.7%)	67 (82.7%)	
Duration of cry					
Mean (±SD)		58.70 ± 57.20	60.11 ± 65.39	39.90 ± 44.13	0.04
Pain Score (NIPS)					
NIPS before procedure					
Mean (±SD)		0.07 ± 0.31	0.11 ± 0.47	0.05 ± 0.31	0.58
NIPS during procedure					
Mean (±SD)		5.80 ± 2.09	5.20 ± 2.13	4.89 ± 2.44	0.03
NIPS change before and during procedure					
Mean (±SD)		5.73 ± 2.07	5.08 ± 2.13	4.83 ± 2.40	0.03
NIPS during procedure category (%)	No pain	11 (13.6)	28 (34.1)	24 (29.6)	0.01
	Pain	70 (86.4)	54 (65.9)	57 (70.4)	

NIPS: Neonatal Infant Pain Scale

Table 3. Least Significant Difference Test for Cry and Pain among 3 groups

Cry (sec)	Groups		P-value
Cry	Group 1	Group 2	0.51
	Group 1	Group 3	0.024
	Group 2	Group 3	0.044
Duration of cry	Group 1	Group 2	0.873
	Group 1	Group 3	0.035
	Group 2	Group 3	0.023
Pain Score (NIPS)			
NIPS during procedure	Group 1	Group 2	0.126
	Group 1	Group 3	0.009
	Group 2	Group 3	0.18
NIPS change before and during procedure	Group 1	Group 2	0.083
	Group 1	Group 3	0.01
	Group 2	Group 3	0.381

NIPS: Neonatal Infant Pain Scale

Group 1: Placebo; Group 2: 5% Glucose; Group 3: 30% Glucose

Table 4. Multivariate Analysis for Factors affecting Pain during the Procedure (NIPS Pain score >3), Enter Method

	OR (95% CI)	P-value
Pain		
Group 2	0.25 (0.11 - 0.57)	0.001
Group 3	0.34 (0.14 - 0.79)	0.01
Gravidity	1.01 (0.84 - 1.21)	0.92
Gender	0.46 (0.10 - 2.15)	0.32
Gestational age	1.30 (0.92 - 1.83)	0.14
Nationality	1.00 (0.55 - 1.80)	1.00
Birth Weight	1.20 (0.40 - 3.56)	0.75
Length	0.83 (0.65 - 1.06)	0.14
Apgar (1min)	3.46 (0.99 - 12.08)	0.05
Apgar (5min)	0.56 (0.13 - 2.48)	0.44
Epidural anesthesia	0.88 (0.45 - 1.72)	0.72
Type of nutrition	0.94 (0.68 - 1.32)	0.73
Duration of last feed	0.88 (0.55 - 1.41)	0.58
Circumcision	2.28 (0.95 - 5.47)	0.06

Variables included: Group (reference: 1); gravidity, gender, gestational age, nationality, weight, length, Apgar (1min, 5min), epidural anesthesia, type of nutrition, duration of last feed, circumcision

Figures

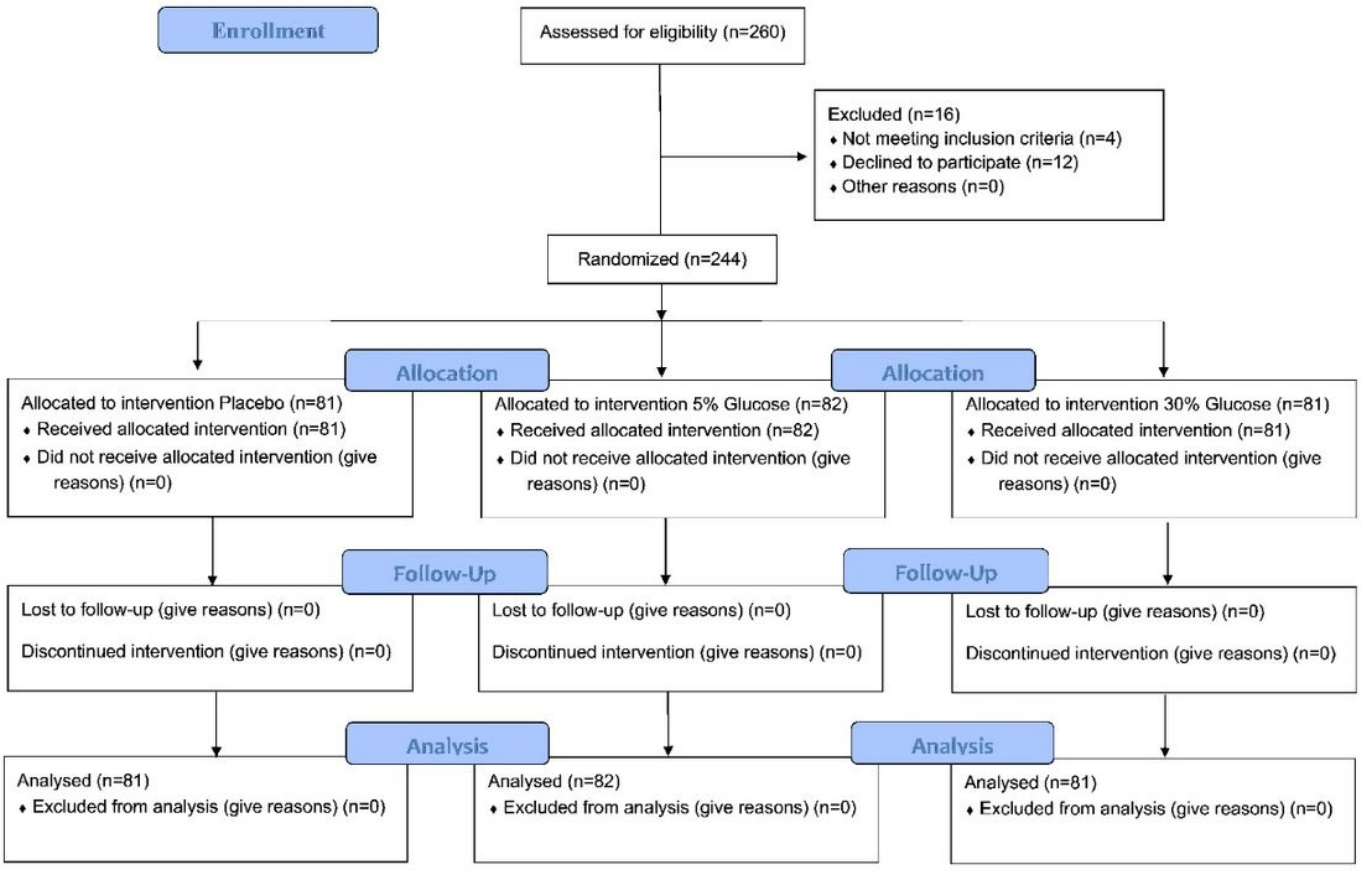

Figure 1

The enrolled neonates were randomly divided into three groups as shown in figure 1.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytablel.docx