ANALGESIC EFFECTS OF GLUCOSE AND WATER IN NEONATES

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Abstract- Several methods have been used to relieve pain in neonates. The objective of this study was to assess the analgesic effect of 50% glucose and water during hepatitis B vaccination. In this randomized controlled trial, 90 term neonates were studied. Infants were randomly assigned to one of the three equal sized groups. First, heart rates were measured by EKG monitor. Then, 2mL of either 50% glucose or sterile water was administered into the mouths of infants in groups one and two, respectively. No intervention was done for group three. During vaccination until three minutes after, crying of babies was taped. Heart rates were measured during injection until 60 seconds. Mean values of duration of crying for glucose, water, and no intervention groups were 21.1 s, 33.3 s, and 56.9 s, respectively, which were significantly different (P= 0.0003). Post hoc test revealed substantial differences between groups one and three (P= 0.0001) and between groups two and three (P= 0.006). However, groups one and two were not statistically different (P= 0.19). Moreover, heart rate did not rise significantly in any of those groups. Both 50% glucose and water showed analgesic effects in neonates.

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INTRODUCTION

Newborns usually undergo painful procedures such as vitamin K_1 injection, blood sampling, and vaccination. Hepatitis B vaccination is a routine painful medical care that is performed in Iran. It has recently been acknowledged that neonates can perceive pain (1, 2). However, until a few years ago, it was claimed that infants do not feel pain (3) and up to the 1980s, analgesics were hardly used even during painful surgeries (4). Indeed, even short term pain can lead to negative effects in neonates (5). Decreased oxygenation, hemodynamic instability, and increased intracranial pressure are short term adverse effects of pain (3-5). Long term outcomes of pain include anxiety, increased sensitivity to pain, sentimental adverse effects and attention deficit hyperactivity disorder (ADHD) (6). Consequences of pain are particularly dangerous to preterm infants because of their immature cerebral vasoregulation (7). In newborns, pain is evaluated by modification in physiological variables (e.g. respiration or heart rate) and changes in behavioral states (*e.g*. duration of crying, facial expression, and limb movements) (8). Treating pain is crucial in neonates both due to ethical reasons and also to prevent negative effects of pain. Several guidelines have been proposed to alleviate pain in infants (9-11). Pain can be relieved by either pharmacological or non pharmacological interventions. Pharmacological treatments are rarely used for short term pain since their effectiveness is controversial and they might also cause some adverse effects.. (12). Simple and benign interventions such as glucose or sucrose solutions (13), sterile water, breast feeding, sucking a pacifier or physical contact between mother and newborn

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(12) can have analgesic effects. Non pharmacological interventions can alleviate pain either directly or indirectly. They directly block nociceptive transmission, activate pain inhibitory pathways, or changes pain modifier system. Moreover they might work indirectly through decreasing sensation of painful stimuli (14).

The objective of this study was to assess the efficacy of 50% glucose solution for pain relief during hepatitis B vaccination in a randomized controlled clinical trial. Majority of previous studies investigated alleviation of pain during venepuncture or heel prick. However, the current study evaluated pain relief during an intramuscular injection. Glucose was selected since it is readily available in the maternity wards and it was used in a few previous studies (15).

MATERIALS AND METHODS

This prospective randomized controlled clinical trial was carried out in the maternity ward of the Mother Hospital in Yazd. The study protocol was approved by the ethics committee of the Shahid Sadoughi University of Medical Sciences. Written informed consents were obtained from mother of all enrolled infants. It should be mentioned that hepatitis B vaccination is a routine medical care for all newborns in Iran and it is totally safe for them.

The inclusion criteria were the following: newborn aged < 24 hours; gestational age 38-42 weeks; birth weight of 2800-4000 g; Apgar score >7 at 5 minutes; and no feeding for the previous 30 minutes. Besides, only newborns delivered by cesarean were included since they had to stay for a longer period in the hospital. Infants were dressed and dry at the time of vaccination. Babies were excluded if they had a medical instability; had previously undergone a painful intervention such as blood sampling, circumcision, or injection; had a congenital disease; or showed signs of serious diseases like septicemia during 24 hours after the procedure.

It was calculated that 30 subjects were needed in each group in order to achieve α=0.05, β=0.1, and accuracy of 35 seconds. We randomly assigned 90 term neonates to one of three groups: group one received 50% glucose; group two were given sterile water; and group three did not receive any intervention. Treatment allocations were inserted in opaque sealed envelopes for the first three infants. Order of treatment was repeated for the rest of neonates until 30 subjects were included in each group. Data was collected by the followings: 1) Questionnaire –It was completed using nursing sheet report and infant's identification bracelet; 2) Tape recorder–For recording infant's voice during injection until three minutes after; 3) EKG monitor-to measure heart rate in 60 seconds.

Participating infants were taken to a quite room with an appropriate temperature. Before vaccination, the observer measured and recorded infant's heart rate and then she left the room. If the participated infant belonged to group one or two, the person responsible for giving solutions would enter the room. Based on the assigned number, either 2 ml of 50% glucose or sterile water was administered in to the newborn's mouth in less than one minute. Administration was done by a 2 ml sterile syringe without needle. This person was blinded to the contents of syringes. In fact, syringes were prepared and coded in the pharmacy department. Two minutes later, the observer and an experienced nurse entered the room and the nurse injected hepatitis B vaccine in the anterior portion of the infant's right thigh by an insulin syringe. The observer taped infant's cry during vaccination until three minutes afterward. Newborn's heart rate was also measured by an EKG monitor during injection until 60 seconds. The observer and nurses were blinded to the type of intervention.

Statistical analysis was performed with SPSS 10 software using one way ANOVA test for the means. Pair wise comparisons of groups were carried out by post hoc analysis. Chi square test was also applied to compare every two groups with each other. *P* value less than 0.05 was considered significant.

RESULTS

From April to October 2004, 90 babies in three equal sized groups were studied. Principal tools to assess pain were duration of crying and heart rate.

As presented in table 1, there were no substantial differences among groups in respect to age, birth weight, sex distribution, Apgar score and heart rate before the procedure. The mean values of duration of crying for group one (50% glucose), group two

Table 1. Characteristic of 90 newborns enrolled in the study

	50% glucose (n=30)	Water (n=30)	No intervention (n=30)
Mean(SD) birth weight(g)	3075(319)	3093(500)	3136(338)
Mean (SD) Apgar at 5 minutes	8.9(0.3)	9.0(0.2)	8.9(0.3)
Boy/ girl	14/19	17/13	15/15
Mean (SD) postnatal age(hr)	14.8(4)	14.9(3.9)	14.7(2.6)

*There was no substantial difference among the groups (P >0.05).

(sterile water), and group three (no intervention) were 21.1 s, 33.3 s, and 56.9 s, respectively. One way ANOVA test disclosed a significant difference among them (p=0.0003). Therefore, post hoc test in LSD form (hypothesizing having equal variances) was used to do pair wise comparison. In our analysis as one way ANOVA was significant, multiple comparison (Tukey, Cheffee and Duncan) gave same results and we called them post hoc. Table 2 shows that significant differences existed between groups one and three (P = 0.006) and between groups two and three (P = 0.006). However, no substantial difference was observed between groups one and two (P = 0.19). The mean heart rate increased by 4, 3.2, and 2.6 beats/min in group one, two, and three, respectively. One way ANOVA test did not reveal any significant difference among the groups in regard to increase in heart rate.

DISCUSSION

For a long time, it was claimed that neonates do not feel pain since their central nervous systems are not fully mature. Nonetheless, it has been recently acknowledged that their neurotransmitters and pain systems are sufficiently mature and complete to perceive pain. In fact, they may even have higher sensitivity to pain and to its long term effects compared with older infants. Unfortunately, treatments to alleviate pain are seldom used in neonates, even though recent studies indicate that treating pain in the newborns are crucial (13).

Table 2. Comparison of mean crying time of groups

Group	Difference in mean crying time(s)	*P* value
Glucose alone	38.5	0.0001
Glucose and water	12.2	0.191
water alone	26.3	0.006

*This table shows that both water and glucose have analgesic effects

Several different scales and methods for assessing pain were applied in previous studies (16). In the present study, duration of crying and increase in heart rate were the principal tools to evaluate pain. Our results showed that both 50% glucose and sterile water were more effective in reducing pain than no intervention. Reduction of duration of crying was substantial in the group given glucose that is in line with other reports (17, 18). The precise mechanism by which glucose relieves pain remains to be identified. It has been suggested that it works through an increase in concentration of β-endorphin by a preabsorptive mechanism (19).

The mean crying time in babies given glucose was about 50% (12 s) lower than the group given water. This difference was not statistically significant, but it might become significant with a larger sample. Our findings indicate that water effectively reduces duration of crying. This could be attributed to the activation of sensory pathways by instillation of water in mouth. Hence, the sensory dominance diverges attention from pain stimuli. Previous studies have also demonstrated the analgesic effects of water (20, 21).

In this study, increase in heart rate was used as another tool to assess pain. However, heart rate did not rise significantly in any of the groups after injection. This implies that increase in heart rate might not be an appropriate measure for pain. Also, another study found that there was no increase in heart rate in babies given either sucrose or placebo (16).

In brief, our results demonstrated that both 50% glucose and sterile water were effective in reducing pain, but a trend towards higher effectiveness was observed with glucose. Since glucose is readily available in hospitals, it is suggested that glucose can be used to provide analgesia during minor painful procedures such as vaccination or blood sampling.

We acknowledge that two potential limitations exist in our study. Firstly choosing duration of crying as an indication of pain probably is not ideal and it is not unique to pain. However, it is an objective method and has less error of measurement. Assessing pain by facial expression and limb movement might be more sensitive, but it is subjective and could be influenced by the observer and causes a bias. Secondly the heart rate measured in 60 seconds but taped infant's cry for three minutes. As the mean time of crying was less than 60 seconds, therefore monitoring the heart rate for 60 seconds can be enough.

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Conflict of interests

We have no competing interests.

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