THE EFFICACY OF ORAL GLUCOSE FOR RELIEVING PAIN FOLLOWING INTRAMUSCULAR INJECTION IN TERM NEONATES

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Abstract- Pain in neonates can be associated with various risks and it seems essential to find a simple and acceptable method for relieving pain. Pharmacologic agents are not recommended in neonates for pain relief in minor procedures but orally administered glucose solution is found to be effective. The objective of this study was to assess the efficacy of oral 30% glucose during intramuscular injection in term neonates. Sixty-four healthy term neonates were recruited for this study during 1 month. The inclusion criteria were gestational age 37-42 weeks, birth weight 2500-4000 gr, and Apgar score > 7. The intervention consists of administration of either 2 ml of oral 30% glucose or 2ml of sterile water 2 minutes before injection. The primary out come measure was the cumulative Neonatal Infant Pain Scale (NIPS) score at 3 minutes after injection. Thirty-two neonates received 30% glucose and 32 neonates received sterile water. The cumulative NIPS score at 3 minutes after injection for neonates given 30% glucose was significantly (P = 0.000) lower than for neonates given sterile water. The heart rate immediately after injection for neonates given 30% glucose was significantly (P = 0.002) lower than for neonates given sterile water. Oral 30% glucose given 2 minutes before injection was effective in reducing neonatal pain following injection. It is a simple, safe and fast acting analgesic and should be considered for minor invasive procedures in term neonates.

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INTRODUCTION

The deleterious effects of pain in infants are fairly well described. They include physiologic and metabolic effects such as vital sign changes, alternation in cerebral blood flow, and outpouring of stress hormones, as well as behavioral changes, memory of the event and potentially negative long-term effects on pain stimuli processing and response (1). Infants may experience more pain with minor procedures than adults do, yet pain management, particularly for procedure- related pain, remain suboptimal (2). Health care practitioners may not accurately interpret an infant's pain signals. Additionally, they may feel that, since opioid administration carries with it the risk of side effects such as respiratory depression, the risks of pain alleviation are not warranted for short-term, mildly painful procedures. The above emphasizes the need to identify effective pain interventions for infants that nurses can implement as an independent practice decision. It is important to anticipate painful experiences while child is hospitalized or receiving medical treatment. Most acute pain experiences in

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medical settings can be prevented or substantially reduced (3). The American academy of pediatrics, in conjunction with the Canadian Paediatric Society, and the American Pain Society developed policy statement addressing the need to minimize painful or stressful procedures and eliminate pain- associated suffering (3, 4). The administration of sucrose or the combination of sucrose with non- nutritive sucking is one of the most frequently studied nonpharmacologic intervention for the relief of procedural pain in neonates (5). Research demonstrates that sucrose can safely and effectively provide analgesia for young infants undergoing painful procedures. It is thought that the analgesic effect of sucrose is mediated via opioid receptors because in animal studies, this effect can be blocked by naloxone (6). The unique response of the neonate to an oral sucrose solution allows for a very safe and effective measure in minimizing procedural pain. More recent studies indicate that 12% sucrose solution may not have the analgesic properties of higher sucrose concentrations; 24% and higher solutions more commonly demonstrated significant findings (7, 8).

The objective of this study was to assess the efficacy of oral 30% glucose during intramuscular injection of vitamin K in term neonates.

MATERIALS AND METHODS

Subjects

Following approval by the Ethic Committee of University of Welfare and Rehabilitation Sciences and informed consent from parents, data were collected from 64 healthy newborn delivered at a hospital in Semnan (Iran). Inclusion criteria were birth weight between 2500 and 4000 grams, age of birth to 24 hours, Apgar scores of at least 7 at 1 and 5 minutes, estimated gestation of at least 37 weeks, heart rate between 100 and 160 per minute, blood O_2 saturation $\geq$ 95% and no known congenital anomalies. Exclusion criteria were Cesarean section receiving vaccination or any injection and birth trauma. They were randomly assigned to 2 groups: intervention and control. The number of samples in each group was 32. Demographic characteristic were essentially homogenous between 2 groups (Table 1). All Apgar scores were > 7 at 1 minute and > 8 at 5 minutes. Mean birth weight was 3262.50 grams (SD = 375.45) and 3139.06 (SD = 309.71) in intervenetion and control groups respectively.

Protocol

Data were collected in a quiet room in the nursery. Infant was brought to a quiet alert state at the start of data collection. The sequence of phases was:

1. Placement of pulse oximeter (NTB195) electrodes and warming device on left hand and the heart rate and blood 02 saturation of blood obtained before intervention.

2. Intervention - 2 ml of oral 30% glucose or 2 ml of sterile water was given to neonates of 2 groups blindly 2 minutes before injection.

3. Procedure- where vastus lateralis muscle was picked up, swabbed and injected with a 30G syringe and 0.5 ml vitamin K pushed in muscle and pressure held with gauze.

4. Three minute post-procedure data collection period for cry, breathing pattern, face expression, arms and legs movements and state of arousal.

5. Immediately and 3 minutes post-procedure data collection for heart rate and blood O_2 saturation.

To minimize variability of the stimulus, the same nurse performed all the injections.

Table 1. Comparing means of background variables between 2 groups*

Variables	Intervention (n=32)	Control (n=32)	*t*	*P*
Birth weight (gr)	3262.50 (± 375.45)	3139.06 (± 309.71)	-1.435	0.156
Gestational age(days)	274.47 (± 6.53)	273.56 (± 7.02)	-0.535	0.595
Apgar,1 min	8.94 (± 0.00)	9 (± 0.24)	1.438	0.156
Apgar, 5 min	9.97 (± 0.17)	10 (± 0.00)	1†	0.321
Birth grade	1.63 (± 0.80)	1.44 (± 0.83)	-1.17‡	0.243
Mother age (years)	25.53 (± 4.91)	23.94 (± 4.97)	-1.289	0.202

* Data are given as mean ± SD.
† Mean of Apgar, 5 min compared with Apgar score=10.
‡ The value is z score of Mann-Whitney test.

Measurements

An experienced nurse reviewed tapes and gave score with NIPS to each neonate. The Neonatal Infant Pain Scale is a behavioral scale and can be utilized in both full term and preterm infants. The tool uses the behaviors that nurses have described as being indicative of infant pain or distress. It composed of six indicators: facial expression, cry, breathing patterns, arms and legs movement and state of arousal. Each behavioral indicator is scored with 0 or 1 except for "cry" which has three possible descriptors; therefore, being scored with a 0, 1, or 2. Infants should be observed for one minute in order to fully assess each indicator. Total pain score ranges from 0-7. The pain levels are: 0-2, mild to no pain; 3-4, mild to moderate pain; > 4, severe pain (9).

Data analysis: Data were analyzed using SPSS for windows. There were no missing data. Descriptive statistics were conducted to summarize sample characteristics. Kolmogorov-Smirnov, independent *t*, Mann-Whitney and Chi square tests were used for analysis.

RESULTS

Background variables

Sixty-four neonates were randomized during the 1-month observation period; similar demographic characteristics were demonstrated between groups (Table 1).

The number of females in intervention and control groups were 16 (50%) and 15 (46.9%), respectively. Infants were born by normal vaginal delivery (without using sedatives) 30 (93.7%) of infants were born by in both groups. To assess the intervention effect on pain the, ordinal logistic regression is used by adjusting the effect of sex.

The background variables had no significant association with pain in both groups (Table 2). Variables had been considered in the model and by using them; the model didn't fit the data well.

NIPS score

The NIPS scores 1 minute before injections were similar in 2 groups. The neonates showed no expression of pain. The NIPS score in the 3 minutes after the injection were markedly higher than in intervention group (P = 0.000) (Table 3). The NIPS scores in control group were significantly higher than intervention group.

To estimate the odds ratio, the severity is considered as the reference category for pain. The results of testing, the fit of the ordinal logistic regression model and proportionality of odds are illustrated in tables 4 and 5, respectively. The model fitted on the data well (P = 0.288) and proportional odds assumption met (P = 0.116). Sex had no significant effect on pain ($0.497 \leq OR \leq 4.047$). The pain decreased significantly in intervention group comparing to control group after intervention (OR=7.345, P = 0.001).

Heart rate

The mean heart rate immediately after injection was markedly higher than before injection in control group. There was significant difference in the mean

Table 2. Association of background variables on pain score in intervention (n = 32) and control (n = 32) groups

Variable	Groups	X^2	df	*P*
Sex	Intervention	2.134	0.144	0.144
	Control	1.242	2	0537
Birth grade	Intervention	2.956	1	0.086
	Control	1.461	2	0.4
Birth weight	Intervention	4.022	2	0.126
	Control	9.099	4	0.059
Gestational	Intervention	0.70	1	0.6
age	Control	1.21	2	0.5
Apgar,1 min	Intervention	-	-	0.345*
	Control	-	-	NC†
Apgar,5 min	Intervention	-	-	0.812[a]
	Control	-	-	NC‡

* Fisher Exact Test.
† Not compatible, all subjects scored 9 for Apgar, 1 min.
‡ Not compatible, all subjects scored 10 for Apgar, 5 min.

Table 3. Analysis of NIPS score in 2 groups (n=32) after intramuscular injection*†

Pain score	Intervention	Control
No pain to mild (0-2)	27 (84.4%)	13 (40.6%)
Moderate Pain (3-4)	5 (15.6%)	7 (21.9%)
Severe pain (> 4)	0	12 (37.5%)
Total	32 (100%)	32 (100%)

*Data are given as number (percent).
† P = 0.000, df=2, X^2=17.23.

Table 4. Testing goodness of fit and proportional odds assumption in ordinal regression.

Test	Chi square	df	*P*
Goodness of fit	5.016	4	0.288
Proportional odds assumption	4.315	2	0.116

increase in heart rate before and immediately after injection between groups ($P = 0.002$) (Table 6).

The mean heart rate 3 minutes after injection was not markedly higher than before injection in control group. There was no significant difference in the mean increase in heart rate before and 3 minutes after injection between groups ($P = 0.86$) (Table 6).

The mean heart rate immediately after injection was markedly higher than 3 minutes after injection in control group. There was significant difference in the mean increase of heart rate immediately and 3 minutes after injection between groups ($P = 0.002$) (Table 6).

DISCUSSION

In this work we assessed the efficacy of oral 30% glucose for relieving pain following intramuscular injection of vitamin K in healthy term neonates measured by cumulative NIPS score, 3 minutes after injection (a minor painful procedure) and 5 minutes after intervention.

Based on the results of this study there were significant differences in pain expression between 2 groups ($P = 0.000$) and in heart rate between 2 groups after minor painful procedure ($P = 0.002$).

So we demonstrated that 2 mL glucose 30% given before intramuscular injection reduced immediate behavioral responses and attenuated the increase in the heart rate that is associated with minor painful procedures.

It is of therapeutic relevance to study pain therapy for minor painful procedures which are performed frequently during neonatal care especially intensive care. Furthermore, neonates are more sensitive to cutaneous stimuli than adults (10) and repeated skin punctures affect their subsequent pain perception (11) and their behavioral and autonomic pain reactions (12).

Solutions of sucrose, glucose, or artificial sweetener given orally before blood sampling are effective in reducing facial and vocal reactions to pain (13-15). The sweet sensory stimulus results in an analgesic effect lasting for about 10 min, *i.e.* well beyond the end of the administration of the sweet solution. Naltrexone can reverse the antinociceptive effects of sucrose in rats (16), and sucrose is not effective in human neonates born to mothers who received methadone during pregnancy (17).

Both observations support the hypothesis that the analgesic effect of sweet solutions is mediated by the release of endogenous endorphins. Previous studies have been criticized because of insufficient standardization of the procedure, and small sample size (13). Therefore, we standardized the procedure to ensure that the stimulus was comparable in intensity and duration and to minimize context influences from comforting co-interventions on the neonatal response, and calculated a sufficient sample size. In the majority of previous studies, the effect of sucrose during a heel-stick was studied.

We decided to study the effect of glucose solution during intramuscular injection. Glucose has the same analgesic effect as sucrose (14), but, contrary to sucrose, glucose is widely used in neonatal care as an intravenous or oral solution, it is more readily available in a hospital, and it does not contain fructose.

Table 5. Parameter estimates for ordinal logistic regression

Parameters	Estimate	SE	df	*P*	OR	95% C ± for OR (Lower, Upper)
Intercept 1	1.707	0.548	1	0.002	5.512	1.883, 16.152
Intercept 2	2.816	0.618	1	0.001	6.712	4.983, 56.094
Group	1.994	0.576	1	0.001	7.345	2.375, 22.738
Sex	0.349	0.535	1	0.514	1.418	0.497, 4.047

Abbreviations: SE, standard error; OR, odds ratio.

Table 6. Testing of increased heart rate before, immediately and 3 minutes after intramuscular injection in 2 groups.

Timing	Group	Means	SD	Dif. Means	Dif. CI (Lower ,Upper)		Paired *t*	df	*P*
Before and immediately after injection	Intervention (n = 32)	-4.34	6.12	-6.64	-2.44	10.49	3.211	62	0.002
	Control (n = 32)	-10.81	9.61						
Before and 3 minutes after injection	Intervention (n = 32)	0.05	4.15	-0.65	1.86	-3.20	-0.51	62	0.86
	Control (n = 32)	0.00	5.89						
Immediately and 3 minutes after injection	Intervention (n = 32)	5.00	5.48	5.81	9.44	2.18	3.201	62	0.002
	Control (n = 32)	10.81	8.68						

Abbreviation: CI, confidence interval.

We found that 2 mL glucose 30% significantly reduced the immediate behavioral pain response rated with the NIPS score after intramuscular injection compared with controls. The influence of the volume of sweet oral solutions on their analgesic effect is unclear. In the majority of studies, an absolute volume of 2 mL sucrose solution was used but effects have been reported for volumes as low as 0.05 mL (18). For glucose solutions, effects have been reported for a volume of 2 mL (14). A 1 mL glucose solution was effective in one study but ineffective in another (19). By increasing the volume of sweet oral solution, the duration of sweet stimulus can be prolonged. Thus, we speculate that 0.4 mL was much less effective than 2 mL because the sweet stimulus was shorter. This explanation is supported by the finding that prolonging the sweet stimulus by repeated doses of 0.05 mL sucrose 24% (20) or 1 mL glucose 30% (19) was more effective than a single dose. In addition to the duration of the stimulus, more intense sweetness also increases effectiveness. Sucrose has an effect at concentrations more than 12% (21) and glucose at concentrations more than 10% (22). Therefore, in clinical trials 25% sucrose or 30% glucose solutions have been used. No gastrointestinal side effects for the single use of these concentrated sugar solutions have been reported so far (13).

Two milliliter glucose attenuated the increases in heart rate. This increase results from the unrest and motor activity induced by the painless handling associated with intramuscular injection in addition to the acute pain stimulus or signifies a stress response that was not influenced by an analgesic alone. It is especially relevant to prevent excess oxygen and energy consumption in sick or preterm neonates with respiratory problems or when the provision of an adequate caloric intake is difficult.

Intramuscular injection increased heart rate significantly in control group. Previous studies of heart rate during minor painful procedures and pain therapy with sweet oral solutions were limited by recording only data for a few isolated time points and by incomplete reporting of the variability of the data. Thus, only two studies of heart rate could be combined in meta-analysis (13), which did not show an effect of sucrose solution on the heart rate response. A sucrose solution that reduced a facial pain score during heel stick had no effect on cardiac autonomic reactivity (23). In conclusion, we conclude that 2 mL oral glucose 30% was an effective pain therapy for intramuscular injection in neonates and mitigated the behavioral responses to acute pain. We recommend that co-interventions for use in combination with sweet oral solutions, like sucking on a pacifier (14, 24), simulated rocking on an oscillating mattress (18), or multisensory stimulation (18), should be explored for their potential to reduce the nonpainful stress of intramuscular injection.

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Conflict of interests

The authors declare that they have no competing interests.

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