ORIGINAL ARTICLE

The Safety and Efficacy of Oral Dextrose for Relieving Pain Following Venepuncture in Neonates

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Summary

The objective of this study was to assess the efficacy and safety of oral 30% dextrose during venepuncture in neonates. Neonates admitted in the Special Care Nursery for jaundice from September 200 to January 2001 were recruited for this double-blind randomised controlled trial. The intervention consisted of administration of either 2 ml of oral 30% dextrose or 2ml of sterile water 2 minutes before venepuncture. The primary outcome measure was the cumulative Neonatal Infant Pain Scale (NIPS) score at 3 minutes after venepuncture and the duration of cry assessed from a videotaped recording. Twenty-six neonates received 30% dextrose and 26 neonates received sterile water. The cumulative NIPS score at 3 minutes (median, IQR) after venepuncture for neonates given 30% dextrose (13, 6.8-21) was significantly (p= 0.03) lower than that for neonates given sterile water (21, 13.8-21). The duration of cry in neonates given 30% dextrose (median 45 sec IQR 1.5-180.8 sec) was significantly (p=0.03) shorter than that in neonates given sterile water (median 191 sec IQR 52.3-250 sec). No neonates developed diarrhoea, fever or rash during the 24 hour observation period. Both the intra-rater (ICC 0.993 95% CI 0.988-0.996) and inter rater (ICC 0.988 95% CI 0.980-0.993) agreement on the 3-minute NIPS score were good. In conclusion oral 30% dextrose given 2 minutes before venepuncture was effective in reducing neonatal pain following venepuncture. It is a simple, safe and fast acting analgesic and should be considered for minor invasive procedure in term neonates.

Key Words: 30% dextrose, Pain, Analgesia, Venepuncture, Neonates

Introduction

Pain as defined by the International Association for the Study of Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage[1]. As babies cannot verbalise the sensation of pain, their plight is often neglected and unattended to during painful procedures. Pain research in the last decade has established that neonates as small as 24 weeks of gestation can experience pain[2]. Factors which may affect the neonate response to pain are maturation of the central nervous system, state of the alertness, duration and type of painful stimuli, the environment and general state of health[3].

Eutectic Mixture of Local Anaesthesia (EMLA) is a commonly used topical anaesthetic in children. However, its slow onset action and its potential toxicity, i.e. methaemoglobinemia in infants less than 3 months of age,[4] makes it impractical to use in the neonatal intensive care unit. Most painful procedures in neonates require a fast and short acting analgesia. This requirement can be met by the use of oral sucrose[5]. However, most studies done so far were related to the use of oral sucrose in heelprick procedures, rather than in venepunctures. The use of sucrose is inconvenient, as a fresh mixture needs to be made regularly to ensure sterility. Studies using commonly available sweet solution such as dextrose are few. Skogsdal *el at* has

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shown that glucose solution normally used for intravenous infusions in hospitals is effective in relieving heel prick pain[6].

The objectives of this study were to assess the analgesic and adverse effects of orally administered 30% dextrose during venepuncture in term neonates and to evaluate the inter-rater and intra- rater reliability of the "Neonatal Infant Pain Scale"[7].

Materials and Methods

A double-blind randomised controlled trial was conducted at the Special Care Nursery ward of Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan from the 18th September 2000 to 18th January 2001. The study population consisted of neonates who were admitted to the nursery for jaundice. Neonates requiring the venepuncture for serum bilurubin, ≥ 24 hours old and with birth weights ≥ 2500g were eligible for the study. Except for jaundice, these neonates were otherwise well. Neonates with major congenital anomalies or neurological deficits, and those who had received analgesic or sedative drugs less than 5 days prior to venepuncture were excluded from the study. All neonates included had no previous venepunctures.

The study was approved by the Research & Ethics Committee, School of Medical Sciences, Universiti Sains Malaysia. Written consent was obtained from parents who agreed to have their babies participate in the study.

The primary outcome measure was the degree of pain induced by venepuncture. The degree of pain in neonates was measured using the "Neonatal Infant Pain Scale"[7] and the duration of cry. The Neonatal Infant Pain Scale (NIPS), a behavioural assessment tool for the assessment of pain in neonates, consists of six behavioural groups: facial expression, cry, breathing patterns, arm movement, leg movement and state of arousal. The score for each behavioural group is shown in Table I. Scores from each behavioural group were added to obtain a total score (maximum 7) at 1 minute, 2 minutes and 3 minutes after the onset of venepuncture. A cumulative NIPS score at 3 minutes was derived by adding the total scores at 1 minute, 2 minutes and 3 minutes giving a range of possible cumulative NIPS score of 0-21. The cry duration, the total sum of audible crying period within the first 5 minutes from the onset of venepuncture, was also measured in seconds. The duration of cry was timed from the outburst of cry until the baby is silent.

The intervention consisted of either 2ml. of 30% dextrose or 2ml of sterile water prepacked in 2ml syringes. After the enrolment of a participant, the investigator would obtain the study medications from a hospital pharmacist, who is aware of the allocation sequence of babies. Venepunctures were performed in a quiet warm room without the presence of the mother and babies were dressed only in diapers. Every effort was made to ensure that the baby was quiet and not crying during the procedure. Babies in deep sleep were gently awaken by the investigator. Study medications were administered orally over 30 seconds. Two minutes after the administration of the oral solution, the dorsum of the hand was cleaned with aqueous chlorhexidine gluconate (1:200) swab and the vein was punctured with a 22G needle. After removal of the needle a cotton swab was applied to the venepuncture site to prevent bleeding. The entire procedure was recorded 2 minutes prior to venepuncture till 5 minutes after venepuncture with a digital video camera (JVC, Japan). After completion of recruitment of all study participants the investigator assessed the degree of pain using the NIPS score and timed the duration of cry on two separate occasions for each baby in random order on a 21 inch screen colour television (Toshiba, Japan). The NIPS score and crying duration were also similarly assessed independently by a second doctor. Variables that may influence pain threshold such as age, sex, height and weight were documented. Potential adverse reactions to oral dextrose, such as diarrhoea (increase in the fluidity and volume of the faeces); sudden outcropping of maculo-papular rash or fever (axillary temperature of ≥38.0 °C) within the first 24 hours of the procedure, were recorded.

The number of neonates needed to achieve 80% power and 5% significance to detect a 2 point difference in NIPS score between 2 groups was 25 infants in each group. Block randomisation (blocks of 4) was used to allocate the participants to dextrose or sterile water. The random allocation sequence was kept by the hospital pharmacist and concealed from the investigator until after the assessment of all outcomes. Data entry and analysis was performed with Statistical Package for Social Sciences (SPSS) Version 10.0 software for personal computers. Differences of baseline characteristics between treatment groups were compared using the t-test for continuous variables and the Fisher exact test for categorical variables. The median cumulative NIPS score at 3 minutes after venepuncture between groups were compared using the Mann-Whitney U test. Intra- and inter-rater agreement of the NIPS score were

analysed by calculating the intraclass correlation coefficient (ICC).

Results

Fifty-two neonates were recruited for the study and there were no withdrawals after randomisation. There were 38 (73%) males and 14 (27%) females. The perinatal characteristics of babies in both groups were comparable (Table II).

The cumulative NIPS score at 3 minutes (median, IQR) after venepuncture for neonates given 30% dextrose (13, 6.8-21) was significantly (p= 0.03) lower than that for neonates given sterile water (21, 13.8-21). Among 3 neonates who scored 0 on the cumulative NIPS score, 2 (7.7%) neonates were from the 30% dextrose group and 1 (3.8%) from the sterile water group. Among 27 neonates who had a maximum score of 21 on the cumulative NIPS score, 18 (69.2%) neonates were from the sterile water group, whereas 9 (34.6%) neonates were from the 30% dextrose group. The percentage of neonates who have a score of 0 on each of the behavioural groupings of the NIPS at 1 minute, 2 minute and 3 minute was higher in the 30% dextrose treatment group compared to the sterile water group (Table III).

The duration of cry in neonates given 30% dextrose (median 45 sec IQR 1.5-180.8 sec) was significantly (p=0.03) shorter than that in neonates given sterile water (median 191 sec IQR 52.3-250 sec). Among 13 neonates who did not cry during the venepuncture, 8 (30.8%) received dextrose, whereas 5 (19.2%) received sterile water. The maximum duration of cry was 290 seconds in the neonates given 30% dextrose and 300 seconds in those given sterile water. Among neonates given 30% dextrose, only 1 (3.8%) cried for 290 seconds, whereas, among neonates given sterile water, 2 (7.7%) cried for 300 seconds.

No baby developed diarrhoea, fever or rash during the 24-hour observation period. Both the intra-rater (ICC 0.993 95% CI 0.988-0.996) and inter-rater (ICC 0.988 95% CI 0.980-0.993) agreement on the 3-minute NIPS score were good.

Table III: Comparisons of percentage of neonates among treatment groups who scored '0' on the NIPS at 1minute, 2 minute and 3minute after venepuncture.

Table I: Neonatal Infant Pain Scale (NIPS) Operational Definitions

Behavioural Group	Score	Features
Facial expression	0	relaxed muscle (restful face, neutral expression
	1	grimaced (tight facial muscle, furrowed brow; chin; jaw)
Cry	0	no cry (quiet, not crying)
	1	whimper (mild moaning, intermittent)
	2	Vigorous cry (loud scream, rising shrill, continuous)
Breathing pattern	0	relaxed (usual pattern for this baby)
	1	change in breathing (indrawing, irregular, faster than usual, gagging, breath holding)
Arms	0	relaxed or restrained (no muscular rigidity, occasional random movement of the arms)
	1	flexed or extended (tense, straight arms, rigid or rapid extension, flexion)
Legs	0	relaxed or restrained (no muscular rigidity, occasional random movement of the legs)
	1	flexed or extended (tense, straight legs, rigid or rapid extension, flexion)
State of arousal	0	sleeping or awake (quiet, peaceful, sleeping or alert and settled)
	1	fussy (alert, restless and thrashing)

Table II: Perinatal characteristics of 56 neonates included in the study

Characteristics	Sterile water (n=26)	30% Dextrose (n=26)	P value
Postnatal age (Days mean, SD)	5.27 (2.32)	5.27 (3.16)	1.00
Boys (Number, %)	21 (80%)	17 (65%)	0.35
Weight (kg mean, SD)	3.02 (0.46)	3.13 (0.50)	0.40
Length (cm mean, SD)	52.38 (2.64)	53.15 (2.14)	0.28
Occipito-fronto circumference (cm mean, SD)	33.0 (1.66)	33.0 (1.38)	0.93
Race (Number, %) Malay	22 (84.6%)	25 (96.2%)	0.35
Others	4 (15.4%)	1 (3.8%)	

Table III: Comparisons of percentage of neonates among treatment groups who scored 'O' on the NIPS at I minute, 2 minute and 3 minute after Venepuncture

	NIPS at1 minute		NIPS at 2 minute		NIPS at 3 minute	
	Sterile water	30% glucose	Sterile water	30% glucose	Sterile water	30% glucose
Facial expression	15%	27%	19%	27%	23%	46%
Cry	15%	38%	23%	38%	23%	54%
Breathing pattern	4%	15%	23%	31%	23%	50%
Arms	4%	12%	19%	27%	23%	50%
Legs	4%	12%	19%	27%	23%	50%
State of arousal	23%	38%	27%	46%	31%	58%

Discussion

The results of this study revealed that 2 ml 30% dextrose had an analgesic effect on Malaysian neonates subjected to venepuncture. There was a 38% reduction of the median NIPS score in the dextrose group compared to the sterile water group at 3 minutes after administration. The median cry duration between treatment groups was 76% less in the neonates given oral dextrose compared to the neonates given sterile water. The significant reduction of pain as measured in both the NIPS and cry duration further substantiate the effectiveness of 30% dextrose in relieving pain in neonates. The NIPS score also has a high agreement within and between observers. This data is in concordance with previous studies[6, 8, 9].

Most studies done on the effectiveness of sucrose as an analgesic showed a reduction in the outcome measures either using a multidimensional behavioural tool or the proportion of time crying. However, Rushforth and Levene[10] reported no significant difference in cry duration among infants given 2 ml 7.5% sucrose 2 minutes before heel prick compared to controls. The dose of sucrose given may not be enough to have an effect as generally a dose of 0.24 g and above is used in studies where sucrose was shown to be effective in reducing pain[5]. In another study, Allen et al[11] also found no significant difference in the "pain- vocalization" of children age between 2 weeks to 18 months old given 0.24 g of sucrose or 2 ml of sterile water 2 minutes prior to immunization. However, the participants in this study were children beyond the neonatal period and the tool for assessment of pain was 'pain-vocalization'. Children in the older age group may require a larger dose of sucrose.

The smaller reduction of pain intensity seen in the NIPS compared to cry duration in this study could be due to an observer tendency not to report the extremes or crying in neonates may not specifically indicate pain. Nevertheless, the 38% reduction of the median NIPS score was comparable to a similar study done by Carbajal et al[8] in which normal full term infants given 2 ml 30% oral glucose before venepuncture showed a 30% reduction in the DAN (Douleur Aiguë du Nouveau-né) scale—a multidimensional behavioural pain scale evaluating facial expression, limb movements and vocal

expression. Similarly, the 76% reduction of the cry duration was comparable to a study done by Skogsdal et al[6] in which neonates given 1 ml 30% oral glucose before venepuncture showed a 75% reduction in the cry duration compared to the control group.

The effectiveness of the 2 minutes interval between glucose administration and venepuncture concurs with the result of other similar studies[6, 8]. The exact mechanism of oral sucrose in pain relief is unknown. Studies done in rats have shown that chronic exposure to saccharin causes morphine tolerance;[12] and that oral sucrose elevates the pain threshold in rats, which is found to be naltrexone reversible[13]. The quick onset of action, that is 2 minutes, indicates that sucrose works even before it reaches the stomach[5]. These findings suggest a link between sweet solution given orally and the endogenous opiod pathway. The oral administration of a small dose of 30% dextrose seems to be a simple non-invasive and valuable intervention to improve analgesia in neonates.

It is known that several types of stimuli, delivered simultaneously with the pain stimulus can induce a reduction in crying and pain related behavioural responses through a mechanism of distraction or interference. Techniques such as tactile stimulation or auditive stimulation are examples of distraction or interference, which may have a calming effect on the neonates. Although this study was conducted in a non sound-proof room, the effect of external stimuli is expected to be similar in both groups. The NIPS score was used in this study because of its simplicity. However, the score was previously validated to discriminate pain in neonates,[7] but not the intensity of neonatal pain. Even though the ease or difficulty of the venepuncture and time taken to collect the required blood sample was not documented there was no venepuncture which was unduly difficult.

No adverse effect of 30% dextrose was observed during the 24 hours observation period in this trial. Willis et al[14] reported that frequent administration (8 to 12 times a day) of small volumes (0.5-1ml) of 20% sucrose mixed with calcium lactate given 20 minutes prior to gavage feeding, could be a contributor to necrotising enterocolitis in very low birth weight infants. It was hypothesized that the hyperosmolality of the undiluted calcium lactate solution led to local trauma of the upper gut wall initiating the pathological process resulting in necrotizing enterocolitis. In a recent study, neonates less than 32 weeks post conceptional age given frequent doses of 0.1 ml of 24% sucrose for every invasive procedure in the first week of life were found to have poorer neurobehavioral development and physiologic outcome[15]. A possible explanation for these poorer neurobehavioral outcomes was cross-sensitisation between dopamine and endogenous opiates. Chronic opioid release due to repeated sucrose administration would repeatedly stimulate dopaminergic neurons that are implicated in locomotor activity and arousal[16].

Conclusion

In conclusion, this study showed that 2 ml 30% dextrose given 2 minute before venepuncture was effective and safe when used for reducing pain following venepuncture in neonates. The oral administration of 30% dextrose should be considered in short painful procedures in neonates as it is a simple, effective, non-invasive, fast acting analgesic which is readily available.

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