

## The effect of two different methods used during peripheral venous blood collection on pain reduction in neonates

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### ÖZET

#### Yenidoğanlarda periferik venöz kan örnekleme sırasında oluşan ağrıyı azaltmada iki farklı yöntemin etkinliği

Bu çalışmanın amacı yenidoğanlarda vene girme sırasında meydana gelen ağrıyı azaltmada emzirme ve sukroz solüsyonunun analjezik etkilerini incelemek ve karşılaştırmaktır. Fenilketonüri (n=26) rutin taraması ve hiperbilirubinemi (n=76) için venöz kan örneği gereken, emzirilen (gestasyon yaşı 38-42 hafta ve doğum kilosu 2500-4500 g) 102 term yenidoğan çalışmaya alındı. Katılımcılar sukroz, emzirme ve kontrol gruplarına ayrıldı. Yenidoğanların sukroz ve emzirme gruplarına ayrılması annelerin isteklerine göre yapıldı. Oysa ki, kontrol grubundaki yenidoğanlara hastanenin rutin uygulaması yapıldı. Yenidoğanların vene girme işlemi öncesi, sırası ve sonrasında ağrıya cevaplarını belirlemek için Yenidoğan Ağrı Skalası (NIPS) kullanıldı ve kalp hızları, oksijen saturasyon düzeyleri ve ağlama süreleri kaydedildi. Ağlama süresi (saniye) kontrol grubuna (103.50±63.69) göre, sukroz (9.56±12.96) ve emzirme (28.62±33.71) gruplarında daha kısa idi. NIPS ile değerlendirildiği zaman, sukroz ile karşılaştırılan emzirmenin analjezik etkisinde bir farklılık olmadığı bulundu. Ortalama kalp hızında, işlem öncesi, sırası ve sonrası 3 grup arasında anlamlı bir farklılık yok idi. İşlem sırasında, sukroz grubunun ortalama oksijen saturasyon düzeyinin kontrol grubuna göre anlamlı derecede daha yüksek olduğu, fakat sukroz ve emzirme grupları arasında farklılık olmadığı gözlemlendi. Bu çalışma emzirme ve oral sukroz solüsyonunun vene girme sırasında yenidoğanlarda ağrıyı azaltmada etkin olduğu bilgisini desteklemektedir.

**Anahtar kelimeler:** Emzirme, sukroz, vene girme, yenidoğan, ağrı, ağrı yönetimi

### SUMMARY

The purpose of the present study was to examine and compare the analgesic effects of breast feeding and sucrose solutions in reducing pain due to venipuncture in term neonates. 102 term infants requiring a venous blood sample for routine screening of phenylketonuria (n=26) and hyperbilirubinemia (n= 76) were included in the study. The participants were allocated into one of the sucrose, breast feeding, and control groups. Allocation of the infants into groups was performed due to mothers' wishes whereas the control group included the infants on whom routine procedures of the hospital were performed. In order to assess the pain response of the neonates before, during and after venipuncture, Neonatal Infant Pain Scale (NIPS) was used and their heart rates, oxygen saturation levels and length of crying were noted. The crying time (seconds) was shorter both sucrose (9.56±12.96) and breast feeding (28.62±33.71) than the control group (103.50±63.69). No difference was found in the analgesic effect of breast feeding compared with sucrose, when assessed with the NIPS. The mean heart rate did not significantly differ among three groups before, during and after procedure. During procedure, the mean oxygen saturation levels of sucrose group were found significantly higher than the control group, but no difference was observed between sucrose and breast feeding groups. This study has confirmed some well known information that breast feeding and oral sucrose solution have pain reducing effects in infants undergoing venipuncture.

**Key words:** Breast feeding, sucrose, venipuncture, neonate, pain, pain management

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## Introduction

Neonates normally undergo various minor painful procedures during their routine daily care. Recent studies have shown that neonates have sufficient anatomical, functional and neuro-chemical structures for feeling pain (Gradin et al. 2002, Wong et al. 1999, Ramenghi et al. 1999, Lawrence et al. 1993). Pain experienced in infancy may have effects later in life such as emotional problems, hyperactivity/attention disorders and defects in social skills (Wong et al. 1999). Previous data suggest that untreated pain early in life may also cause deleterious effects on the developing central nervous system (Gradin et al. 2002, Logan 1999, Bucher et al. 1995, Taddio et al. 1994). The number of painful stimuli needs to be kept in minimum and every effort should be made to render them less painful. Various simple methods effectively reduce the pain response of newborns undergoing routine procedures, such as heel lancing. Swaddling, holding and providing the oral tactile stimulation of sucking on a pacifier are effective nonpharmacologic approaches (Bellieni et al. 2002, Gormally et al. 2001, Campos 1994, Johnston and Strada 1986). Administration of sucrose with or without nonnutritive sucking (via pacifiers) has been the most frequently studied nonpharmacologic intervention for relief of procedural pain in neonates (Greenberg 2002, Horwitz 2002, Stevens et al. 2001, Abad et al. 2001, Overgaard et al. 1999, Blass et al. 1999, Stevens et al. 1997, Haouari et al. 1995). Oral sucrose is effective and reliable in relieving pain in minor procedures (Kaufman et al. 2002, Bellieni et al. 2002, Anand 2001, Bauer and Versmold 2001, Masters-Harte and Abdel-Rahman 2001, Bucher et al. 1996). The effects of both sucrose and nonnutritive sucking are thought to be mediated by the endogenous opioid and nonopioid systems but the underlying mechanisms may differ (Blass 1997, Gunnar et al. 1984). In neonates, the pain relieving effect of oral sucrose is enhanced when combined with parental holding, stimulated rocking or multisensory stimulation. On the other hand the most effective dosage of oral sucrose and the best way of giving it are still being investigated (Horwitz 2002, Mitchell et al. 2000, Ramenghi et al. 1996). Recent studies have demonstrated that certain tastes and flavors alleviate newborn pain. As little as 2 ml of milk with its fat and protein components (Blass 1997; Blass 1997) or sweet substances reduce pain in human and rat infants and eliminate spontaneous crying as well (Stevens et

al. 2001, Ramenghi et al. 1999, Overgaard and Knudsen 1999, Carbajal et al. 1999, Haouari et al. 1995). It has also been reported that skin-to-skin contact between mother and infant during suckling leads to decrease in stress and oxygen consumption, strengthens the tie between mother and infant, helps the maintenance of body temperature, improves cardio-respiratory stability and sleep form and provides behavioral adaptation to new conditions (Carbajal et al. 2003, Gray et al. 2002). Gray et al. (2000) found effective skin to skin contact in reducing pain experienced during heel lance. Although Blass (1997) has shown that milk and some of its components are antinociceptive in newborns, Örs et al. (1999) have reported that 25% sucrose solution was significantly more effective than breast milk. Bilgen et al. (2001) have shown that 25% sucrose is superior to breast feeding in pain relief, which is reflected mainly in crying time and behavioral variables. The antinociceptive effect of nonnutritive sucking has also been widely studied (Franck 1998, Blass 1994).

The Cochrane trials register has at least 2 trials Bilgen et al. (2001) (sucrose, expressed breast milk and breast feeding, heelprick) and Carbajal et al. (2003) (breast feeding vs glucose plus pacifier, venipuncture). Analgesic effects of breast feeding during heel pricks were studied previously (Carbajal et al. 2003, Gray et al. 2002, Bilgen et al. 2001), however the results are contradictory possibly due to methodological differences. There is no study in the literature investigating the analgesic effects of sucrose and breast feeding on venipuncture related pain.

The purposes of the study was to investigate and compare the analgesic effects of breast feeding and sucrose solutions in reducing pain due to venipuncture.

## Material and Method

### *Sample Selection*

One hundred and two healthy, breastfed infants (gestational age 38-42 weeks and birth weight 2500-4500 g) requiring a venous blood sample for routine screening of phenylketonuria and hyperbilirubinemia were included in the study which was conducted in Akdeniz University Hospital between June and July 2002. Exclusion criteria were age over 42 days, presence of an illness, a fasting period less than one hour, parental reluc-

tance to participate, and failure to take the blood sample at once.

### *Sample Description*

The participants were allocated into one of the sucrose (n=34), breast feeding (n=34), and control (n=34) groups. Allocation of the babies into sucrose and breast feeding groups was performed due to mothers' wishes whereas the control group included the babies on whom routine procedures of the hospital were performed.

### *Heart rate and oxygen saturation*

A pulse-oxymeter (Nellcor N180) probe was placed on the first toe of the right foot of the each infant in three groups just before the venipuncture. Heart rate and oxygen saturation levels were continuously observed throughout the procedure. The highest observed levels before, during and after the venipuncture were recorded.

### *Duration of the venipuncture and crying*

The duration of the venipuncture (in seconds), from the beginning of needle insertion to the placement of the plaster, was measured by the researcher. The amount of crying time (in seconds) was also noted. For this purpose crying beginning from onset after the needle insertion until all crying activity had ceased, up to a maximum of three minutes (since some newborns continued to cry for longer than 3 minutes), was recorded on audio tape (Sony M-529V Micro cassette recorder) and later analyzed by the same researcher. Total length of crying was defined as the total time during which the subject produced audible distress vocalizations during the 3-minute observation period (Lewindon et al. 1998).

### *Pain responses*

Pain responses were assessed with the Neonatal Infant Pain Scale (NIPS). This scale was developed to provide an evaluation of procedural pain or distress in a full-term or preterm newborn and can be used in newborns up to 6 weeks of age. The tool consists of 6 categories (facial expression, cry, breathing patterns, arms, legs, state of arousal), scored dichotomously, with 2 descriptors in each category. The total score ranges from 0 to 7. Pain assessments were made at baseline (before the procedure), during (when maximal response was observed), and after the procedure

(when plaster was applied). This tool evaluates multiple behavioral indicators; thereby assessing a variety of responses the newborn may exhibit (Lawrence et al. 1993). NIPS was translated into Turkish by Akdovan and validity and reliability of the scale was confirmed by the same author in a study on 180 infants (Akdovan 1999). Preprocedural, procedural and postprocedural Cronbach alpha coefficients were found 0.83, 0.83 and 0.86 respectively. A NIPS form was prepared for each baby considering the methodology used in previous studies (Shah and Ohlsson 2002, Lawrence et al. 1993). These forms were completed by the same research nurse who observed the infants before, during and after the venipuncture.

### *Procedures*

Approval from the Ethics Committee of Akdeniz University was granted to perform the study. The aim, risks and possible benefits of the study were explained to the mothers and informed consent was obtained from each.

All the babies were taken into a warm and quiet room. Their clothes were taken off and soiled diapers were changed. All venipunctures were performed by the same nurse who is experienced in blood sampling. The nurse slightly pressed on and cleaned the skin of the dorsal aspect of one hand with alcohol to make the target vein clear and then took the venous blood sample inserting a 24 gauge needle. A sticking plaster was placed onto insertion site after the needle was taken out. All infants were awake at the time of the procedure.

The standard clinic procedure for infant injection was implemented in control group. According to this procedure the infant was wrapped in a blanket with only the hand that would be used for the injection outside the blanket and placed on the treatment table. The mother stayed next to the infant and tried to soothe him/her verbally during and after the blood collection period. The infant was cuddled by the mother just after the injection and given a pacifier if he/she is a user.

In both of the sucrose and breast feeding groups, the mothers seated and reclined on a comfortable chair with the infants in their arms after taking off clothes and changing soiled diapers.

Sucrose group: Mothers were instructed to hold their infants across their laps in a cross-cradle position to allow infants' hands accessible for

peripheral venous blood collection throughout the procedure. They were also asked to talk and maintain eye and bodily contact with their babies before, during and after the venipuncture. The daily prepared 2 ml of 25 % sucrose solution was put into pacifiers (Wee) by a research nurse. The dosage of the solution was adjusted upon recommendations of previous studies (Horwitz 2002; Anand 2001, Stevens et al. 1997, Ramenghi et al. 1996). A new pacifier was used for every infant and they were allowed to continue sucking after sampling. The babies started to suck the pacifier with 2 ml of sucrose 3 minutes before the venipuncture and went on sucking after sampling. Mothers were warned not to let the pacifier drop while the babies were crying.

Breast feeding group: The mothers cradled their infants in a breast feeding position allowing maintaining full-body, skin-to-skin contact during the entire procedure. A large amount of areola was placed into baby's mouth and three minutes after the first jaw movements were observed the venous blood was taken. Infants were breast feeding during and after the venipuncture. The mothers were asked to continue breast feeding their infants even if they started to cry during and after the procedure. If the infant left the nipple the mothers were encouraged to try to get the infant to take it again.

### Data analysis

It was determined that 34 babies would be sufficient in each group to achieve the 80 % power ( $\alpha=0.05$ ) to show a 30 % reduction in crying time. In addition to calculating distribution and mean values in the groups, the individual differences between NIPS scores, duration of crying, heart rate, oxygen saturation levels and other variables

(infant gestational age, postnatal age and weight) were analyzed by the One-Way variance analysis and the Posthoc Scheffe tests. The difference between sucrose and breast feeding groups was analysed by Mann Whitney U test. A  $p$  value less than or equal to 0.05 was considered to be statistically significant.

### Results

Of the participants, 58 (% 56.9) were male and 44 (% 43.1) were female. The mean gestational and postnatal ages were  $39\pm1.5$  months and  $16.8\pm12.6$  days respectively. The mean birth weight was  $3326.4\pm434.4$  g and the mean length was  $50.1\pm2.3$  cm. The mean postnatal age of the sucrose infants was  $12.2\pm12.5$  days, the breast feeding infants was  $18.3\pm11.3$  days and the control infants was  $15.6\pm14.4$  days. The mean gestational age of the sucrose infants was  $38.9\pm1.1$  weeks, the breast feeding infants was  $38.9\pm0.9$  weeks and the control infants was  $39.1\pm1.1$  weeks. The mean birth weight of the sucrose infants was  $3202.5\pm360.0$  g, the breastfeeding infants was  $3327.5\pm409.8$  g and the control infants was  $3381.6\pm434.3$  g. The mean delivery (vaginal:cesarean) of the sucrose infants was 11:23, the breast feeding infants was 20:14, the control infants was 16:18. There were no significant differences between the groups in terms of gestational age, postnatal age, and birth weight ( $F=0.40$ ,  $p=0.670$ ;  $F=0.61$ ,  $p=0.544$ ;  $f=1.77$ ,  $p=0.176$ ;  $x^2=4.81$ ,  $p=0.090$ , respectively) (Table 1).

Venous blood samples were taken from the sucrose group for phenylketonuria ( $n=9$ ) and hyperbilirubinemia ( $n=25$ ), the breast feeding group for phenylketonuria ( $n=4$ ) and hyperbilirubinemia ( $n=30$ ) and the control group for phenylketonuria ( $n=13$ ) and hyperbilirubinemia ( $n=21$ ). All the babies were breastfed; one baby

**Table 1.** Demographic characteristics of the groups.

	Sucrose (n=34)	Breast feeding (n=34)	Control (n=34)	F	p
Postnatal age (d)	17.2 ± 12.5	18.3 ± 11.3	15.6 ± 14.4	0.40	0.670
Gestational age (wks)	38.9 ± 1.1	38.9 ± 0.9	39.2 ± 1.1	0.61	0.544
Weight (g)	3202.5 ± 360.0	3327.5 ± 409.8	3381.6 ± 434.3	1.77	0.176
Delivery (vaginal:cesarean)	11:23	20:14	16:18	4.81	0.090*

Note: Abbreviations: SD=standard deviation, g=gram, wk=week, d=day.

\* Chi-square test

**Table 2.** Total duration of crying time and NIPS scores.

	Sucrose (n=34)	Breast feeding (n=34)	Control (n=34)	F	p
Crying time	9.6 ±12.9	28.6 ± 33.7	103.5 ± 63.5	47.31	0.000
NIPS Score					
<i>Before procedure</i>	0.0 ±0.0	0.0 ± 0.0	0.2 ± 0.8	104.2	0.036
<i>During procedure</i>	1.2 ± 1.3	1.9 ± 1.9	6.4 ±1.6	90.98	0.000
<i>After procedure</i>	0.3 ± 0.9	0.9 ±1.9	5.6 ± 2.2	3.43	0.000

in sucrose group and 5 babies in control group were taking infant formula in addition to mother's milk.

The mean crying time was significantly longer in control group than that of sucrose and breast feeding groups (Table 2). The mean crying time was also found longer in breast feeding groups than that of sucrose group (Mann Whitney U test,  $p=0.009$ ).

Cronbach Alpha reliability coefficients for NIPS measurements before, during and after the procedure were found 0.76, 0.92 and 0.95 respectively. Mean NIPS score in control group was significantly higher than those of sucrose and breast feeding groups before the venipuncture. This difference in favor of intervention groups was found to be persisting both during and after the procedure (Table 2). However, no difference was found between the NIPS scores of sucrose and breast feeding groups (Mann Whitney U test, during procedure  $p=0.133$ ; after procedure  $p=0.169$ ). The mean heart rate did not significantly differ among

three groups before, during and after procedure (Table 3).

The mean oxygen saturation levels of three groups were not significantly different from each other before the procedure. During procedure, the mean oxygen saturation levels of sucrose group were found significantly higher than the control group, but no difference was observed between sucrose and breast feeding groups (Mann Whitney U test,  $p=0.240$ ). After procedure, the mean oxygen saturation level of sucrose group was found significantly higher than both breast feeding and control groups (Table 3).

### Discussion

We found a decrease in venipuncture related pain in both of the sucrose and breast feeding groups compared to the control group. These analgesic effects may be related to ingredients of sucrose solution and breastmilk as well as nutritive or non-nutritive sucking and full body contact. Sweet taste, milk, and fat flavor-induced analgesia in rats have been blocked by low doses of nal-

**Table 3.** Mean heart rates and oxygen saturation levels.

	Sucrose (n=34)	Breast feeding (n=34)	Control (n=34)	F	p
Heart rate/min					
<i>Before procedure</i>	147.8 ± 16.3	148.7 ± 14.6	141.9 ±13.7	2.12	0.126
<i>During procedure</i>	157.3 ±16.5	156.0 ± 15.2	151.8 ± 35.3	0.48	0.618
<i>After procedure</i>	157.3 ± 16.5	153.2 ± 18.4	153.3 ± 27.1	0.01	0.987
O <sub>2</sub> saturation level (%)					
<i>Before procedure</i>	98.0 ± 2.1	96.9 ±2.9	97.3 ± 2.0	1.85	0.162
<i>During procedure</i>	97.8 ± 2.0	96.2 ± 3.6	93.9 ± 5.7	7.93	0.001
<i>After procedure</i>	97.9 ± 2.2	95.7 ± 3.1	94.5 ± 3.6	11.43	0.000

trexone, suggesting opioid involvement (Blass 1988, Blass 1987). Some authors suggested that the effects of sucrose and non-nutritive sucking might be mediated by both the endogenous opioid and nonopioid systems and these mechanisms may be additive or synergistic (Blass 1999, Gunnar 1988). The fat, protein and other ingredients of mother's milk stimulate opioids and block pain fibers running down to the spinal cord (Gray et al. 2002). It was also shown that milk and fat have a postgastric antinociceptive effect that is mediated through the release of the gut hormone cholecystokinin (Weller 1988). The quieting effects of milk and fat are highly attenuated in rats by devazopide, the cholecystokinin type-A receptor antagonist (Blass and Shide 1993). Non-pharmacologic approaches of pacifier and holding were also theorized to act via the activation of endogenous opioid pathways (Anand 2001).

Although pain reducing effects of sucrose or pacifier+sucrose in invasive procedures have been widely investigated so far, number of studies testing the combined effect of pacifier, sucrose and parental holding is low (Bellieni 2002, Johnston 1997). Additionally, there is no consensus on the most effective dose of sucrose and the best way of giving (Gibbins et al. 2002, Horwitz, 2002, Anand 2001, Mitchell et al. 2000, Ramenghi et al. 1996). Regarding high analgesic effect observed in our sucrose group, one may recommend using 25% of sucrose solution via pacifier. This approach provides an additive effect of sucking even the sucrose ingredient of pacifier is depleted.

Gray et al. (2002) reported that breast feeding before, during and after heel prick markedly reduced crying and grimacing and prevented the increase in heart rate in term neonates compared with swaddled infants in their cots. Their results are highly similar to ours. Our study adds an additional comparison of these effects with those of sucrose solution. To our knowledge, there have been very few previous reports comparing the analgesic effects of sucrose and breast feeding. Probably because of some methodological or applicational differences between previous studies and ours, we found different results in comparison of breast feeding and sucrose solution. Örs et al. (1999) found 25% sucrose solution superior to breast milk. Similarly, Skogsdal et al. (1997) reported that, strong sweet solutions such as sucrose and 30% glucose alleviated pain successfully whereas breast milk did not. In a later study Bilgen et al. (2001) allowed breast feeding

for two minutes and stopped before a heel prick. They found this type of intervention ineffective possibly due to cessation of breast feeding before the procedure. In our study infants continued suckling during and after the procedure and this might have provided an additional analgesic effect of sucking alone. In a similarly designed study to ours, Carbajal et al. (2003) compared the effects of breast feeding and glucose and reported no difference between median pain scores for breast feeding and glucose plus pacifier groups, similar to our study. The main difference between their and our study methods is lack of full body contact in their glucose administering style. They did not use pacifier and did give the solution while the infants were lying on the table alone. However, it is well known that skin to skin contact is effective in reducing pain although its mechanisms are not known. Both sucking and taste-induced analgesias are of rapid onset. In contrast, contact-induced analgesia is of a gradual onset and 10 to 15 minutes of contact were required to prevent excessive crying and grimacing (Gray 2000).

This study has confirmed some well known information that breast feeding and oral sucrose solution combined with full body contact have pain reducing effects in infants undergoing venipuncture. Additionally, we found that breast feeding was as effective as sucrose in alleviating pain contrary to majority of previous reports. Further studies are needed to test or clarify the effectiveness of breast feeding considering ideal suckling duration and maternal anxiety.

One limitation of our study is lack of a third intervention group to test the effects of full body contact alone. Presence of such a group would help us better understand contribution level of skin contact to analgesic effects of sucrose or breast feeding. Future studies should be designed considering this limitation. Furthermore, regarding the fact that contact effectiveness is highly dependent on the relaxation level of holding person (Gray 2000), measuring anxiety level of her/him might be helpful to standardize analgesic effects among different subjects. Another limitation was lack of concealment in randomization process of two intervention groups. Participants were allocated into sucrose or breast feeding groups regarding their desire. This might have had some positive effects on mothers such as reduced level of anxiety, but we recognize that this is a methodological flaw. Observational nature of the NIPS scoring is another problem of reliability, but the

other physiologic indicators such as heart rate or oxygen saturation level are also highly speculative to explain pain reactions of the infants.

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