COMPARISON OF ANALGESIC EFFECTS OF EMLA CREAM AND ORAL GLUCOSE DURING VENIPUNCTURE IN ICTERIC NEWBORNS

M. Noori-Shadkam[1*] and M. H. Lotfi[2]

1) Department of Community Medicine, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

2) Department of Epidemiology, Health Faculty, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

Abstract- A number of studies has shown that orally administered sweet-tasting solutions reduce signs of pain during painful procedures. The local anesthetic cream EMLA has recently been shown to be safe for use in neonates. The present study aimed to compare the pain-reducing effect of EMLA cream with that of orally administered glucose during venipuncturing in newborns. A randomized, controlled, double-blind Clinical trial was done on the 220 newborns undergoing venipuncture for clinical purposes. One hundred- six of the newborns received EMLA on the skin and orally administered placebo (sterile water) and 114 received orally glucose 30% and placebo (Vit A+D) on the skin. Symptoms associated with pain while venipuncturing measured by Neonatal/ Infant pain scale (NIPS) and crying time were compared between two groups. There were no differences in background variables between the 2 groups. The results showed that the NIPS scores were significantly lower in the glucose group (median: 2) compared with the EMLA group (Median: 3) (P= 0.000). The duration of crying in the first 2 minutes was significantly lower in the glucose group (median: 2 sec) than in EMLA group (median: 9 sec) (P< 0.01). 12.3% and 29.2% of neonates in glucose and EMLA groups had NIPS above 3 respectively where the observed difference was found to be statistically significant (P< 0.05). Our study showed that compared with EMLA cream, orally administration glucose can be more effective, tolerable and convenient in reducing of pain resulting from venipuncturing in neonatal period.

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Key words: Neonatal/Infant pain score; EMLA cream; oral glucose

INTRODUCTION

There are some unavoidable situations in which invasive procedures should be applied for the purpose of neonatal cares. Venipuncture is the most routine way that is used for the both healthy and unhealthy babies.

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*** Corresponding Author:**
Mahmood Noori Shadkam,Department of Community Medicine, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Tel: +98 351 7247074, 913 3535419
Fax: +98 351 7247074
E-mail: mahmood_7072005@yahoo.com

There are enough experiments showing there are anatomical and physiological potency in babies for understanding pain (1, 2). Recent investigations suggest that experience of pain in the neonatal period affects the next period of life (3, 4). Venipunture is the recommended method for the purpose of blood taking in full-term babies (5). Compared with ankle sampling, venipuncture has some gains such as obtaining enough volume of blood, less amounts of pain and more success rate (6-8). An appropriate sampling technique may be useful in pain reducing, however, it is suggested that for the reducing stress created by venipuncture, a pain-reducing method

may be used (7). Numerous studies show which administration of orally sweet-tasting solutions relief signs of pain during painful procedures (9-11). This can be due to two reasons: 1) releasing of endorphins and 2) the mechanism of pre-absorption of sweet-tasting (12, 13). EMLA cream is a local pain reducer consisting of Lidocaine and prilocaine. It has been shown that using EMLA cream 60 minutes before venipuncturing can be lead to reduce pain feeling in humans (14). Moreover, the recent investigations have shown that EMLA has no harmful effect in neonates where it is using in the most countries such as Sweden (15-17). In respect with orally glucose solutions of 30%, studies have indicated that it has no harmful effect and easily can be tolerated by neonates (8).

While time period for the effectiveness of oral glucose is immediate, EMLA cream take time about 60 minutes. Therefore, its usefulness has limitations in the acute situations (18-20). The pain reducing effects of EMLA cream and orally glucose solution have been separately investigated. However, there are a few researches in which their effects together have been compared (21). The present study aimed to compare the pain reducing effects of EMLA cream and orally administrated sweet-tasting solution resulting from Venipunture on the neonates suffering from icter admitted to Shahid Sadoughi hospital of Yazd city affiliated to Shahid Sadoughi University of Medical Sciences.

MATERIALS AND METHODS

The present double blind Randomized Clinical Trial (RCCT) was conducted in Shahid Sadoughi hospital situated in Yazd city, Yazd province, Islamic Republic of Iran between October 2004 and June 2005. The main purpose of study was to compare the relief effects of EMLA cream and orally administrated sweet-tasting solution in reducing pain resulting from Venipunture in the neonates suffering from neonatal icter. All full term neonates (≥38 weeks) in age range of > 1day and <15 days admitted to hospital were studied. For the purpose of billirubin measurement, they had to undertake a venipunture. Babies with neurologic symptoms, gestational age <38w, given a history of consumption of sedatives or pain reliving medicines 24 hours before admission and neonates who had no consent form were excluded from study. Data from an earlier study (25) was used to estimate the sample size where σ_1=7.5 (standard deviation of crying time in EMLA group) and σ_2=6.7 (standard deviation of crying time in glucose group) were considered. We were interested in detecting whether orally administrated glucose can reduce significantly at least 3 seconds (d=3/sec difference) reduction in the mean of crying time, using study power of 0.90 (β=.20) and (α=.05, two-tailed). A total sample size of 180 (90 for each group) was obtained. Considering an increase of 25%, finally 230 subjects were studied. Then, subjects randomly assigned to two different trials groups (115 each). Group I) at first, 0.5 g EMLA cream (14) was smeared on the back side of hand followed by closed dressing. After 60 minutes, dressing was removed.

To reduce venous contraction and any stress in babies, venipuncture was delayed for a time period of 15 minutes. In this group, 1cc sterile water, as placebo, was poured into the subject's mouth by syringe five minutes before sampling. Group II) the similar approach was considered for the subjects in group II, but trial and placebo for this group were 1cc glucose %30 [8] and 0.5 g plasebo ointment respectively. Venipunture was done by a needle 21-gauge followed by bandage on the sampling point. Then, for two minutes evaluation in a low stress condition, neonate was placed on the nursery bed. Each neonate had only a chance to include in study. Duration of crying and response to pain were scored by Neonatal /Infant Pain Scale (NIPS) (21) where the scale measured changes in six parameters including face appearance, crying, respiratory status, movement in upper and lower extremities and alertness status within two minutes started from venipunturing. The highest and lowest score given to subjects were 7 and zero respectively where the highest value was correlated with the highest response to pain. A score of less than or equal 3 was considered as painless or mild grade of pain. The tools of enquiry were a pre-coded questionnaire and clinical evaluation.

Analysis was done by SPSS software package using appropriate non-parametric statistical tests such as Chi-squared for the categorical and Mann-Whitney U Test for the numeric variables.

Table1. Demographic and biomedical data of subjects in two groups

Variable	Group I (n= 106)	Group II (n=114)	*P*
Sex			
Male	58 (55)	55(48.5)	
Female	48 (45)	59(51.5)	NS
Mean Age (days)	4 (2-15)	4.2 (2-15)	NS
Mean Weight/g (SD)	3250 (2350-4560)	3257 (2340-4450)	NS
Mean Bilirubin mg/dl, (SD)	11 (6-22.5)	10.5 (6.5-23)	NS

RESULTS

In this study, a total of 10 neonates due to unsuccessful Venipunture and not meeting the research procedures were excluded from study (9 subjects in group I and one in group II). 51 (48%) and 67 (59%) of neonates in both groups were females respectively where no significant discrepancy was seen in respect with sex between two groups. In addition, using student t-test it was seen that there was no significant difference between mean of age, weight and levels of serum bilirubin in subjects of two groups (Table 1).

Using non-parametric Mann-Whitney U Test, it was found that the median of NIPS score in group II was significantly lower than that in group I (2 vs. 3, $P = 0.000$.) Moreover, applying the same statistical test showed that median crying time per second (measured within the first two minutes after venipunturing) in the neonates of group II was shorter than in group I (2 sec versus 9 sec) where this discrepancy was seen to be statistically significant ($P < 0.01$) (Table 2).

29% and 12% of neonates in groups I and II had a NIPS score of more than 3 respectively and this difference also was seen to be highly significant ($P = 0.000$). Three neonates in group I showed a real erythema on the prescription place of EMLA cream but no such phenomena was seen in none of the neonates in group II.

DISCUSSION

Documents show that orally glucose can reduce pain created by venipunturing in neonates (8). Recently, it has been shown that EMLA cream also has similar property (14, 22, 23).

Quantitative studies, however, have compared efficacies of these in reducing of pain in neonates. Our study, which is probably the first randomized clinical trial aimed to compare the effect size of orally administrated glucose and EMLA cream in reducing pain in Iranian neonates, shows that orally glucose compared with EMLA cream can be more effective. NIPS (neonatal/infant pain score) and time of crying within two minutes were used as criteria in comparison of these two methods as the values were lower in group receiving orally glucose than in group received EMLA cream. This is in accordance with findings of two separate studies carried out by Eriksson and Abad *et al.* where neonates receiving orally glucose had lower scores of pain and crying times compared to those received EMLA cream (8, 26). In these studies, no harmful effect was seen while giving orally glucose 30%. In another study done on 201 neonates by Gradin *et al.* in Sweden also pain scores and crying times were lower in glucose group (25). In this study lidocain was more effective than in orally glucose in reducing of crying time in neonates (27).

Table 2. Median of crying time period and pain score in two groups

Variable	Group I (n = 106)	Group II (n = 114)	*P*
Median of time crying period /sec	9 (0-70)	2 (0-75)	< 0.01
Median of pain score /NIPS	3 (0-10)	2 (0-9)	< 0.001

There was no side effect in relation to consumption of orally glucose in our study. This was also seen in study carried out by Maria G *et al.* in which glucose solution of 30% was used (25). Similar studies also show that full-term babies can easily undertake orally glucose without any side effect.

It is known that although repeated low dose of sucrose has useful effect on the premature babies, but it should be studied in mature babies (10). Three neonates in our study showed a moderate erythema in the prescription place of EMLA cream. This has also been shown by other studies (14, 21). Another preference for the using of orally glucose relative to EMLA cream is that blood sampling can be done immediately after prescription. This is useful in acute conditions in which time saving is important.

On the other hand, use of EMLA cream can make a limitation in repetition of Venepunture (14) and its repeated doses increase the chance of met-heamoglobinemia (23). Therefore, there are various studies in which the use of orally glucose due to less harmful, more effective and time saving compared to EMLA has been recommended (8,14, 22, 23). No study is available in which the effect of concomitant consumption of EMLA cream and orally glucose has been investigated so it needs more examinations in the next.

In conclusion, our study showed that compared with EMLA cream, orally administration glucose can be more effective, tolerable and convenient in reducing of pain resulting from Venepunture in neonatal period. This may be explained by the fact that orally glucose can act as a stimulator for the releasing of endorphin in central nervous system leading to better control of pain than EMLA cream which is a local pain ameliorator. Main limitation in our study was a problem in relation to providing EMLA cream since it is made from France so there is not enough amounts of medicine in our country. However, low levels of budget and lack of cooperation shown by some neonate's parents were other limitations seen within study period.

Conflict of interests

The authors declare that they have no competing interests.

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