

Original Research Article

Eutectic mixture of Prilocaine and Lignocaine (2.5%) versus 5% Lignocaine versus placebo for pain relief in new-borns undergoing venipuncture: a hospital based, double blind randomised case control study

Rakshith Reddy H. V.*, Aswathy Rajan, Amitha Rao Aroor

Department of Pediatrics, A J Institute of Medical Sciences, Mangalore, Karnataka, India

Received: 27 February 2019

Accepted: 05 March 2019

*Correspondence:

Dr. Rakshith Reddy H. V.,

E-mail: rakshithreddy19@gmail.com

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ABSTRACT

Background: Venipuncture is one of the most common cause of iatrogenic pain in neonates which is equally stressful to the parents as well as to the personnel performing the procedure. Despite an abundance of data that demonstrate the efficacy of local anesthetics for reducing venipuncture pain in neonates their use in day to day practice is not used widely used. Our objective was to evaluate the efficacy of EMLA cream and 5% Lignocaine cream versus placebo for pain relief in newborns undergoing venipuncture.

Methods: Present study was a hospital based, double blind randomised, case control study. A 240 eligible new-borns were randomised into EMLA, 5% lignocaine and placebo groups after randomization. The respective creams were applied 1 hour before the procedure and pain scores were assessed using NIPS scoring during venepuncture. Data was analysed using SPSS ver. 20.0 statistical package. Student's unpaired t-test and paired t tests was used to compare continuous data, and to compare pain scores one-way ANOVA was used to compare categorical data. A p-value <0.05 was considered statistically significant.

Results: Paired t-tests revealed significant lower NIPS scores in EMLA and 5% lignocaine group than the placebo group (p value=0.001).

Conclusions: From present study it can be concluded that both EMLA and 5% lignocaine are equally efficacious and cost effective in reducing the pain of venepuncture in neonates.

Keywords: EMLA, 5% Lignocaine, Neonates, Pain, Venepuncture

INTRODUCTION

The neonatal nervous system even though immature can perceive pain.¹ Venipuncture is one of the most common cause of iatrogenic pain in neonates which is equally stressful to the parents as well as to the personnel performing the procedure.² Robust responses to painful stimuli were often dismissed as physiologic or behavioral reflexes and not related to the conscious experience of pain.¹ Studies done between 2007 and 2012 have shown that not treating pain can lead to short-term complications

as well as long-term physiologic, behavioral, and cognitive sequelae, which included altered pain processing, impaired executive functions, attention-deficit disorder and impaired visual perceptual ability.²⁻⁴ Use of currently available techniques such as topical anesthetics can significantly decrease the burden of distress associated with venepuncture in neonates.⁵

Eutectic mixture of local anaesthetic (EMLA) cream is a topical anaesthetic mixture of lidocaine (2.5%) and prilocaine (2.5%) in a cream base.⁶ Lignocaine inhibits

axonal transmission by blocking sodium channels. Its use has demonstrated effectiveness in decreasing pain response to immunizations.² These agents have been found to decrease pain during venipuncture, percutaneous central venous catheter insertion, and peripheral arterial puncture.⁷ The aim of the present study was to evaluate the effectiveness of implementing EMLA cream vs 5% lignocaine cream vs placebo for local application as a routine pain-relieving measure in neonates undergoing venipuncture for either diagnostic or therapeutic purpose.

METHODS

A hospital based prospective, double blinded, randomized controlled study was conducted at A.J. Institute of Medical Sciences, Mangalore, Karnataka over a period of 3 months between May 2018 and July 2018. The study protocol was approved by A.J. ethics committee of A.J. Institute of medical sciences, Mangalore, Karnataka, India

Inclusion criteria

- All term newborns admitted to our ward and neonatal intensive care unit undergoing venipuncture either for sample collection or intravenous cannulation/medication were included in present study.

The parents/legal guardian of the neonates who agreed to participate in the study was required to fill a written informed consent for the same.

Exclusion criteria

- Authors have excluded preterm babies, neonates requiring positive pressure ventilation, diagnosed with sepsis or birth asphyxia as EMLA required 1 hour, post application for the effective action,
- Neonates with an open wound at the intended site of application also have been excluded. Receipt of an analgesic/anesthetic/sedative with 12 hours before venipuncture was also excluded.

The neonates were to receive one of the following creams one hour prior to procedure:

- Eutectic mixture of local anesthetic (EMLA®) containing 2.5% lidocaine and 2.5% prilocaine
- Placebo
- 5% lignocaine.

The placebo cream was an inert cream which could not be visually differentiated from EMLA cream, 5% lignocaine cream contained plain lignocaine only. Blinding was done by the pharmacist unknown to present study by transferring the 3 creams used for the study into identical sterile containers which were marked as A, B and C by him. The containers were then handed over to the observer and used for the study. The eligible neonates

were randomly divided into the 3 groups, sequentially i.e. the first neonate to group A, the second to group B, the next to group C and so on. Post randomization, the designated cream was applied to the chosen venipuncture site of approximately 1 cm² which was approximately 1 gram, by trained resident doctors/nurses who were blinded to the cream by the means of pharmacist, giving the creams labeled as A, B, C in sterile containers. After a waiting period of 1 hour prior to the prick, the residual cream was wiped off with a sterile gauze/cotton swab and the area was disinfected with chlorhexidine solution. Venipuncture was done using a 21-gauge needle. A baseline heart rate, respiratory rate, saturation and level of alertness (Table 1), were recorded just prior to the prick. A 30 second video recording was done for all the neonates from the time of prick for the purpose of assessing pain by the same observer for all the newborns. Pain was assessed at the time of prick by scoring on Newborn infant pain scale (NIPS).⁸ According to this scale a score greater than 3 indicated the presence of pain. A score of 0-2 was considered to be no pain/mild pain, 3-4 indicated mild to moderate pain and >4 indicated severe pain.

Statistical analysis

Statistical analyses were performed using the SPSS ver. 20.0 statistical package (SPSS Inc., Chicago, IL, USA) for windows. Demographic data was expressed as mean and standard deviation. Student's unpaired t-test and paired t tests was used to compare continuous data, and to compare pain scores one-way ANOVA was used. A P-value <0.05 was considered statistically significant.

RESULTS

A total of 300 babies were assessed for eligibility during the study period, out of which 60 were excluded as per the exclusion criteria.

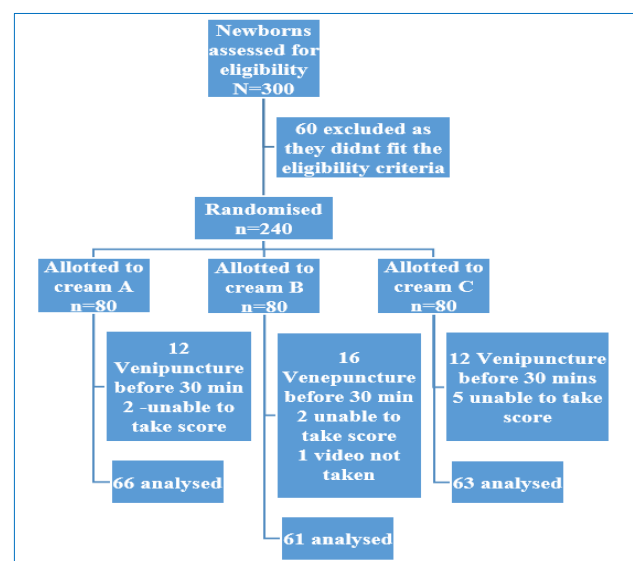


Figure 1: Consort diagram.

The rest of the 240 were randomized to receive one of the 3 creams. A total of 190 newborns completed the study, out of which 66 newborns received EMLA cream and 61

newborns received placebo and the remaining 63 babies, 5% lignocaine as shown in consort diagram (Figure 1).

Table 1: Demographic data.

Demographic parameter	EMLA	Placebo	5% Lignocaine	P value
Age (hours)	77.5±24	69.9±20	73.3±25	0.187
Birth weight (kg)	3.0±0.3	3.0± 0.3	2.94±0.41	0.521
Sex (n (%))				
Males	34 (48.5)	33 (50.8)	33 (52.4)	0.985
Females	32 (48.5)	30 (49.2)	30 (47.6)	
Mode of delivery (n (%))				
LSCS	28 (48.5)	30 (49.2)	30 (47.6)	0.199
NVD	38 (57.6)	32 (50.8)	42 (66.7)	
Level of alertness	3.51±1.71	3.18±0.17	3.22±1.79	0.369

Table 2: Mean and standard deviation of pre and post procedure vitals.

Vitals	EMLA	Placebo	5% lignocaine	P value
Pre-procedure				
HR	141.3±3.2	141 ±4.4	139.4±3.4	0.11
RR	42.27±2.4	42.5±2.5	41.9±2.2	0.437
SPO ₂	97±0.24	98±0.8	97±0.35	0.443
Post-procedure				
HR	141.12±2.9	147.7±4.3	142.2±2.5	<0.01
RR	44.7±2.47	44.34±2.37	44.5±2.12	0.578
SPO ₂	96.7±1.4	96.75±1.468	97.27±1.27	0.55

Table 3: NIPS score comparison.

	EMLA	Placebo	P value
Mean	2.4±1.46	5.7±1.2	<0.001
	5% lignocaine	Placebo	
	2.5±1.4	5.7±1.2	<0.001
	EMLA	5% lignocaine	
	2.4±1.46	2.5±1.4	0.540

Authors found that, age, sex, birth weight and mode of delivery were similar in all three groups suggested by the lack of significant difference in the demographic and baseline data amongst the three groups as shown in (Table 1).

Pre and post venepuncture vitals were recorded as shown in Table 2. Although a difference in the heart rate, respiratory rate and saturation was detected among the 3 groups before the procedure, the values were comparable between the 3 groups with no statistical significance.

However, it is interesting to note that the RR, SPO₂ values prior to venepuncture and post venepuncture in the EMLA, 5% lidocaine and placebo groups remained similar with no change while there was a significant increase in heart rate ($p>0.01$) in placebo group.

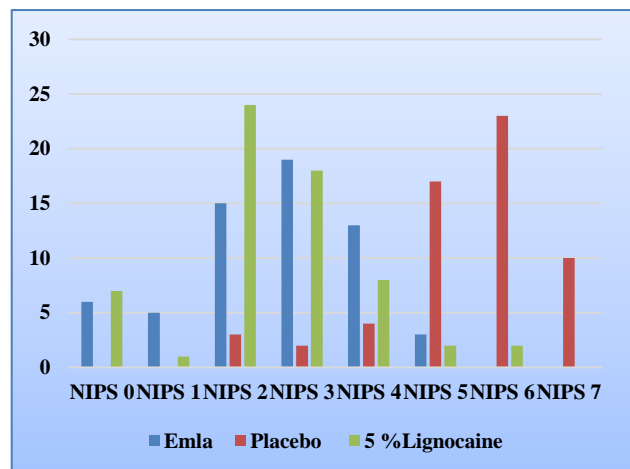


Figure 2: Comparison of NIPS score in EMLA, 5% lignocaine and placebo group.

Authors also found that level of alertness did not significantly affect the pain scores ($p = 0.369$). On analyzing NIPS scale in both the groups, there was a significant reduction in the mean score value in newborns receiving EMLA, 5% lignocaine cream over the placebo, with the p value <0.001 which was statistically significant, and both the creams were equally effective over the placebo cream with p value <0.001 .

DISCUSSION

Understanding of pain in neonates have made many important advances in last 2-3 decades.⁸ Effective pain management has now become a standard of care for all newborns as this has been found to possibly improve their clinical and neurodevelopmental outcomes.⁹ Routine evaluation and management of neonatal pain has progressed to become an imperative therapeutic goal in the twenty-first century. Topical anaesthetics are proven to be effective for some types of procedural pain such as venous cannulation or venipuncture.⁹ Present study provided evidence that both EMLA and 5% lignocaine cream were equally effective in reducing pain in neonates undergoing venepuncture. Authors have included only term babies although there is evidence of the effect of these creams in preterm babies.¹⁰ In a study done by Lindh et al, on assessment of EMLA vs placebo on heart rate during venepuncture in neonates, they had found that the placebo group had significantly higher heart rates over the EMLA group.¹¹ Similarly, in present study there was no significant difference in respiratory rate and saturation amongst any of the 3 groups but there was significant increase in heart rate in placebo group compared to the study groups. However median heart rate and oxygen saturation recorded in placebo and EMLA in a study done by Acharya et al, also did not reveal any significant changes.¹² Gradin et al, compared term neonates who were given oral glucose or EMLA cream for pain reduction during venepuncture, which showed no significant difference in changes in the heart rate between the groups in spite of an overall increase in heart rate.¹³ An earlier study done by Woodman PJ et al on newborns undergoing circumcision, 30% lidocaine cream application prior to the procedure showed decrease in the mean peak heart rate as compared to placebo.¹⁴ In the study done by Sabety F et al, pulse rate and respiratory rate analysed in term infants undergoing venipuncture with lidocaine gel application showed significantly higher pulse rate in the placebo group when compared to lidocaine group while no change was seen amongst the two groups in respiratory rate during the procedure which was similar to present study.¹⁵ Rade et al, conducted a study in Iran in the year 2004-2005, where he showed that the effect of lidocaine ointment was significantly more effective than breastfeeding and placebo.¹⁶ In fact, lidocaine was found to be more effective than oral glucose in reducing crying time in neonates.⁶ It was recommended in the consensus statement for the prevention and management of pain in the newborn, for application of EMLA cream to the proposed site when

non-urgent before percutaneous venous catheter insertion.¹⁷ In present study a significant reduction in NIPS score with EMLA group as well as in 5% lignocaine group was determined when compared with the placebo group. The efficacy of EMLA in reducing overall injection pain is likely attributable to a decrease in pain as the needle penetrates the skin, as well as a reduction in the underlying muscle spasm that is associated with such pain.⁹ The pain-relieving effect of EMLA was more pronounced at the time of the needle prick.¹⁸

This has been shown in a systematic review conducted by Taddio et al, which concluded that EMLA cream reduced pain during circumcision in newborn and it was found to be effective and safe.¹⁹ However, Woodman PJ et al, showed that there 5% lignocaine -prilocaine combination was more effective in attenuating the behavioural and physiological indicators of neonatal pain than 30% lidocaine alone.¹⁴ Median NIPS score assessed in a study done by Shadkam et al, also revealed a value of 3 which is higher than the average NIPS score in both our EMLA as well as lidocaine group.²⁰ However, Acharya et al, used neonatal facial coding system score for pre and post venipuncture analysis of pain in preterm infants showed that median values were almost comparable in placebo and EMLA groups.¹² A study done by Chen et al enrolled 32 premature infants and compared scores of the 'Neonatal pain, agitation and sedation scale' (N-PASS) of each enrolled preterm infant before, during and 10 min after venipuncture without and with EMLA cream use.

A significant decrease in N-PASS scores during venipuncture in infants with EMLA cream.¹⁸ In the study published by Cleo K et al, Hardin done on 145 children, and the pain scores were measured using FPS-R Score, it was found that in children having venipuncture at the antecubital fossa, lidocaine given 2-3 minutes before venipuncture to the epidermis using a rapid, needle free, drug system safely reduced pain.²¹ Present study showed that compared with placebo, EMLA cream as well as 5% lignocaine cream were equally effective in reducing pain from venepuncture in neonatal period and none of the neonates had any adverse reactions to the EMLA cream or 5% lignocaine cream. There is not much data to suggest an appropriate dose of EMLA cream for venipuncture in preterm/term infants.¹⁵

Authors found EMLA and 5% lignocaine cream weighing 1 g covering an area of 1cm² was adequate to produce effective response. The use of EMLA and 5% lignocaine in neonates has procured varied results. Variability in skin perfusion and thickness, need of different doses and application timing in neonates need to be considered. Areas with thinner skin have increased vascularity and require a shorter application time as longer application time may result in rapid clearance of the drug from the dermis and prevent sufficiently high concentration of the drug around the nerve endings.¹⁰

CONCLUSION

As indicated by NIPS score, new born infants do feel pain during venipuncture, and both EMLA and 5% lignocaine are cost effective, safe and are very effective alternative for alleviating pain in neonates undergoing venipuncture and hence either EMLA or 5% lignocaine cream can be used can be recommended before the venipuncture in the neonates.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Anand KJ, Hickey PR: Pain and its effects in the human neonate and fetus. *N Engl J Med.* 1987;317(21):1321-9
2. Ferguson SA, Ward WL, Paule MG, Hall RW, Anand KJ. A pilot study of preemptive morphine analgesia in preterm neonates: effects on head circumference, social behavior, and response latencies in early childhood. *Neurotoxicol Teratol* 2012;34(1):47-55.
3. De Graaf J, van Lingen RA, Simons SH, Anand KJ, Duivenvoorden HJ, Weisglas-Kuperus N, et al. Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: five-year follow-up of a randomized controlled trial. *Pain.* 2011;152(6):1391-7.
4. Grunau R, Tu MT, Anand KJ, Stevens B, McGrath P. Pain in neonates and infants. *Elsevier Sci.* 2007(3):45-55.
5. Schechter NL, Zempsky WT, Cohen LL, McGrath PJ, McMurtry CM, Bright NS. Pain reduction during pediatric immunizations. evidence-based review and recommendations. *Pediatr.* 2007;119(5):e1184-98
6. Taddio A, Manley J, Potash L, Ipp M, Sgro M, Shah V. Routine immunization practices: use of topical anesthetics and oral analgesics. *Pediatr.* 2007;120(3):e637-43.
7. Hall RW, Anand KJ. Pain management in newborns. *Clinics Perinatol.* 2014;41(4):895-924.
8. Witt N, Coynor S, Bradshaw H. A guide to pain assessment and management in the neonate. *Curr Emergency Hosp Med Rep.* 2016;4:1-10.
9. Unruh AM. Voices from the past ancient views of pain in childhood. *Clin Perinatol.* 2014;41(4):895-924.
10. Lemyre B, Hogan DL, Gaboury I, Sherlock R, Blanchard C, Moher D. How effective is tetracaine 4% gel, before a venipuncture, in reducing procedural pain in infants: a randomized double-blind placebo-controlled trial. *BMC Pediatr.* 2007;7:1471-2431.
11. Lindh V, Wiklund U, Håkansson S. Assessment of the effect of EMLA® during venipuncture in the newborn by analysis of heart rate variability. *Pain.* 2000;86(3):247-54.
12. Acharya AB, Bustani PC, Phillips JD, Taub NA, Beattie RM. Randomised controlled trial of eutectic mixture of local anaesthetics cream for venepuncture in healthy preterm infants. *Archives Dis Childhood-Fetal Neonatal Ed.* 1998;78(2):F138-42.
13. Gradin M, Eriksson M, Holmqvist G, Holstein H, Schollin J. Pain reduction at venipuncture in newborns. Oral glucose compared with local anesthetics cream. *Pediatr.* 2002; 110 (6):1058-63.
14. Woodman PJ. Topical lidocaine-prilocaine versus lidocaine for neonatal circumcision: a randomized controlled trial. *Obstet Gynecol.* 1999;93:775-9.
15. Sabety F, Yaghoobi M, Torabizadeh M, Javaherizadeh H, Haghighizadeh MH, Muhammadian F. Which is better for pain reduction before venipuncture: glucose, lidocaine or expressed breast milk. *J HK J Paediat.* 2013;18:19-23.
16. Malekan Rad E, Momtazmanesh N, Barkatin R. The effects of glucose, breast milk and lidocaine cream on acute pain of arteriopuncture in term neonates. *KAUMS J.* 2004;8(2):15-9.
17. Anand KJ. Consensus statement for the prevention and management of pain in the newborn. *Archives pediat Adolesc Med.* 2001;155(2):173-80.
18. Chen FH, Lin CH, Line CS, Ling TT, Jung WL, Hsing T, et al. The Effect of EMLA cream on minimizing pain during venipuncture in premature. *Infants J Tropic Pediat.* 2013;59(1):72-3.
19. Taddio A, Stevens B, Craig K, Rastogi P, Shlomi T B ,et al. Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. *N Eng J Med.* 1997;336:1197-120.
20. Nouri SM, Lotfi MH, Aarafi H. Comparison of the effect of local anesthetic cream and orally administered glucose solution in reduction of pain in icteric newborns during venipuncture. *IRCMJ* 2007; 9(2):93-9.
21. Hardin C. Epidermal lidocaine safely reduced pain in children having venipuncture at the antecubital fossa. *Evidence-based Med.* 2005;10(6).

Cite this article as: Reddy RHV, Rajan A, Aroor AR. Eutectic mixture of Prilocaine and Lignocaine (2.5%) versus 5% Lignocaine versus placebo for pain relief in new-borns undergoing venipuncture: a hospital based, double blind randomised case control study. *Int J Contemp Pediatr* 2019;6:1014-8.