International Journal of Contemporary Pediatrics
Sharma R et al. Int J Contemp Pediatr. 2022 Jul;9(6):529-535
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20221369

Original Research Article

Comparison of effect of eutectic mixture of local anesthetics, amethocaine and 4% lignocaine in alleviating pain during venous cannulation in children up to three years

Rakesh Sharma, Pancham Kumar, Ambika Sood, Satendra Gupta*

Department of Paediatrics, Indira Gandhi Medical College Shimla, Himachal Pradesh, India

Received: 10 February 2022
Revised: 03 March 2022
Accepted: 28 April 2022

***Correspondence:**
Dr. Satendra Gupta,
E-mail: drsatendra54@gmail.com

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ABSTRACT

Background: Intense anxiety experienced by the parents and their children regarding venous cannulation may result in non-adherence to the recommended procedure. The aim of present study was to compare the effects of eutectic mixture of topical anesthetics, amethocaine and 4% lignocaine on pain responses during venous cannulation in children up to 3 years.
Methods: The present hospital based, prospective, randomized comparative study was conducted from December 2019 to November 2020 at KNH and IGMC, Shimla. The study population was divided in to two groups, group I (less than one month) and group II (one month to three years) and were further divided into three groups (amethocaine, EMLA and 4% lignocaine). NIPS and FLACC score for 3 events (pre procedural, immediately after cannulation and three minutes after cannulation) were noted.
Results: 99 children were enrolled in our study (59 in group one and 40 in group two) and all were fulfilling inclusion criteria. NIPS score was highest for lignocaine before, immediate and after cannula followed by EMLA and was least for amethocaine. FLACC score was highest for lignocaine before, immediate and after cannulation. FLACC score was lowest for amethocaine, immediately and after cannulation and for EMLA before cannulation.
Conclusions: Amethocaine significantly reduces the pain response as compared to EMLA and 4% lignocaine group specifically immediately after cannulation and three minutes post cannulation.

Keywords: Comparison, EMLA, Amethocaine and 4% lignocaine, Pain during venous cannulation, Children up to 3 years

INTRODUCTION

Peripheral venous cannulation is a routine procedure during the delivery of anesthesia, which many adults find painful. Inadequate pain relief is not only unpleasant for patients but may cause anxiety about further treatment, deter patients from seeking medical care in the future, and result in increase in heart rate and blood pressure.[1]

Several experts suggest that the neonate's expression of pain does not fit within the strict definition of the International association for the study of pain because of the requirement for self-report. Neonates cannot verbalize their pain, they depend on others to recognize, assess and manage their pain. Several validated and reliable pain measures exist to assess acute pain in term and preterm neonates.[2]

Venipuncture is commonly seen as one of the most painful and frequently performed invasive procedures. In the pediatric population, venipuncture can be one of the most distressing events associated with medical encounters. Many different products, such as eutectic mixture of local anesthetics (EMLA) cream, have been evaluated for their ability to decrease this pain. EMLA cream is an oil-water emulsion of lidocaine and prilocaine, which is applied in a mound over the venipuncture site and covered with a semipermeable dressing, where it is absorbed into the patient's skin. The mixture is termed eutectic, because the crystalline bases mix to create lower melting points than what would be achieved individually, creating ideal circumstances for skin penetration. Manufacturers recommend an application time of 60 minutes, which allows the anesthetic to hinder initiation and conduction of nerve impulses that cause pain.[3]

The neural pathways for pain may be traced from sensory receptors in the skin to sensory areas in the cerebral cortex of new born infants. The density of nociceptive nerve endings in the skin of new born is similar to or greater than that in adult skin.[4]

Neonatal infant pain scale (NIPS) is a behavioral assessment tool to measure pain. The scales takes into account pain measurements before, during and after painful procedures scored in one minute intervals. The indicators include: face, cry, breathing pattern, arms, legs and state of arousal. Results are obtained by summing up the scores for six indicators (where 0 indicates no pain and 2 indicates pain), with maximum score of 7.

The faces legs activity cry consolability scale (FLACC), is a behavioral scale for post procedural pain in young children. It includes 5 indicators (face, legs, activity, cry and consolability) with each item ranking on a three-point scale (0-2) for severity by behavioral descriptions resulting in total score between 0-10. It is used in children from 2 months to 7 years. EMLA cream is a topical anesthetic mixture of lidocaine (2.5%) and prilocaine (2.5%) in a cream base. Amethocaine is an ester local anesthetic which is more lipophilic than either lignocaine or prilocaine, facilitating its passage across the stratum corneum. In a 4% preparation, it has a more rapid onset of action of 30 min after application with occlusive dressing, lasts 4-6 h, causes slight erythema which may aid cannulation, and can be used in infants from 1 month of age. Lignocaine, commonly referred to as lidocaine, is an amide local anesthetic agent and a class1b anti arrthymic. Lignocaine is considered effacious, safe and cost effective for any health care system. It has anti-inflammatory, immune-modulating and analgesia effect. Many studies were done in the past comparing the analgesic effect of EMLA, amethocaine and 4% lignocaine in children, but most of them are done in the older age group and only compared two analgesic agents. To address the above-mentioned issue our study was done in the neonates and children under three years of age. Our study compared the analgesic effect of all the three drugs simultaneously. Previously done studies have proved all the three agents to have potent analgesic effect and therefore control was not taken in our studies. Age-appropriate pain score was used. NIPS was used for neonates and FLACC was used children under 3 year's age.

METHODS

Study design, location and sample size

Current was a tertiary hospital based, prospective, randomized comparative study among children from birth to 3-year age in department of paediatrics, Kamla Nehru state hospital for mother and child Shimla and IGMC Shimla. The study was done over a period of one year. The study was conducted in the department of paediatrics, Kamla Nehru state hospital for mother and child Shimla and IGMC Shimla Taking confidence interval at 95%,power of study as 90% and mean and SD of EMLA group as (2.6±1.8) versus mean and SD of 4% lignocaine as (1.9±1.5) from study done by Smith et al and mean and SD of EMLA group as (2.4±1.2) versus mean and SD of amethocaine as (2.3±1.6) from study done by Newbury et al the sample size came out to 99, that is, 33 in each group (EMLA group versus 4% lignocaine group versus amethocaine group). The sample size was calculated using OPEN EPI statistical software.[5]

Inclusion criteria

Inclusion criteria for current study were all the term newborn babies born at Kamla Nehru hospital during the study period plus all children up to age 3 years coming at IGMC Shimla requiring venous cannulation.

Exclusion criteria

Exclusion criteria for current study were gestation less than 37 weeks; IUGR baby; newborn born to those mothers who receive any drug which cause CNS depression in the baby; newborn whose parent/guardians refuse to give the consent for the study; newborn and children with having any skin allergy or local infection at site of injection, newborn or children with a history of allergy to local anesthetic or to any component of EMLA cream, received analgesic, anesthetic or sedative less than 12 hours before the time of procedure, congenital or idiopathic methaemoglobenemia; those on antiarrhythmic agents such as calcium channel blockers and beta blockers, analgesic use 24 hours before venous cannulation; newborns with any major congenital malformations and more than one attempt at cannulation.

Data collection

The data related to demographic profile; maternal history of any chronic illness would be recorded as per a structured case recording format. Enrolled cases were

divided into two groups, group 1: less than 1 month, group 2: more than 1 month. The study groups were further divided in following 3 groups. Group 1 which included infant plus children who were cannulated after application of EMLA cream. Group 2 which included infant plus children who were cannulated after application amethocaine cream. Group 3 will include infant plus children who were cannulated after application 4% Lignocaine cream.

Venous cannulation was done at the same state of arousal to all the neonates (at stage IV), at the same surrounding and at the same examination table, after half to one hour of feeding. Pre cannulation NIPS and FLACC score were taken in all cases. All the cannula was administered by the same person gently. EMLA cream. 5 gm were uniformly applied to an area of 1cm square in at cannula area and covered with an occlusive dressing (Tegaderm) for 30 minutes, the dressing was removed immediately before procedure, the skin was wiped dry, disinfected. Cannulation was done using 18G cannula. The pain was assessed using NIPS and FLACC pain scale in group one and group two respectively, at the base line prior to the cannulation, immediately after the cannula and at three minutes after introduction of cannula. Similar procedure was done using amethocaine cream and 4% lignocaine cream applied for same duration of time serially on the patient requiring venous cannulation.

Statistical analysis

Statistical analyses were performed using Epi info version 7 software. Results on continuous measurements were presented on mean±SD and categorical as frequency (percentage). Normality of the data was assessed using Shapiro Wilk test/Kolmogorov-Smirnov test. Inferential statistics like Chi-square test/Fischer exact test, Kruskal Wallis test was used to check difference between the three groups. Friedman's test was used to compare the variables within a group over a period of time. The significance of level adopted was 5%.

RESULTS

A total of 99 children were included in the study. Study group was divided into two parts as pain scale used in neonate was NIPS and pain scale used between two months to three years was FLACC. Group I included 59 neonates and group II included 40 children between 2 months to three years in which EMLA, amethocaine and 4% lignocaine cream was applied. The children in both the group was further divided. The study was done at department of pediatrics at K. N. H and I. G. M. C Shimla. Mean age of study population was of (0.35±0.14) months for group one and 14 months for group two (14.17±7.22). The mean age for EMLA, amethocaine and 4% lignocaine in group one was (0.35±0.13) months, (0.35±0.15) months and (0.35±0.15) months respectively. The mean age for EMLA, amethocaine and 4% lignocaine in group two was (15.00±6.94) months, (13.92±7.19) months and (13.54±8.03) months respectively. Mean weight of study population for group one was (3.03±0.43) kg and (9.31±2.74) kg for group two. The mean weight for EMLA, amethocaine and 4% lignocaine in group one was (2.99±0.41) kg, (3.02±0.41) kg and (3.09±0.48) kg respectively. The mean weight for EMLA, Amethocaine and 4% Lignocaine in group two was (9.82±2.57) kg, (9.27±2.77) kg and (8.80±3.00) kg respectively.

Table 1: Age, gender and weight distribution among participants.

Parameters	Group 1 (mean±SD)	Group 2 (mean±SD)
Age (years)		
EMLA	0.35±0.13	15.00±6.94
Amethocaine	0.35±0.15	13.92±7.19
4% lignocaine	0.35±0.15	13.54±8.03
Weight		
EMLA	2.99±0.41	9.82±2.57
Amethocaine	3.02±0.41	9.27±2.77
4% lignocaine	3.09±0.48	8.80±3.00
Gender N (%)		
EMLA		
Female	09 (45)	06 (42.9)
Male	11 (55)	08 (57.1)
Amethocaine		
Female	08 (40)	03 (23.1)
Male	12 (60)	10 (76.9)
4% lignocaine		
Female	07 (36.8)	07 (53.8)
Male	12 (63.2)	06 (46.2)
Overall		
Female	24 (40.7)	16 (40)
Male	35 (59.3)	24 (60)
Total	59 (100)	40 (100)

When compared between the three groups prior to cannulation**,** majority of the patients in three groups were having mild pain. Six patients in EMLA and 4% lignocaine group were relaxed when compared to 11 patients in amethocaine. Fourteen patients in EMLA group had mild pain followed by twelve patients in 4% lignocaine group and nine in amethocaine. Only one patient in 4% lignocaine group had moderate pain while none was present in other groups. When assessed between the groups immediate after cannulation, majority of the patients were in mild pain. None of the patient were having moderate pain in amethocaine group while four patients in EMLA and six patients in 4% lignocaine group suggestive of Amethocaine being more efficacious. After three minutes of cannulation, one patient each in EMLA and 4% lignocaine group had moderate pain while it was none in amethocaine group. Statistically significant difference was observed only for immediate after cannulation between the groups. However, when checked within a group, it was significant for EMLA, amethocaine

and 4% lignocaine. Amethocaine was more effective in alleviating immediately after venous cannulation (3.25±0.64) and three minutes post cannulation (0.95±1.05) compared to EMLA and 4% lignocaine as evident by lower mean±SD for the group.

Table 2: Comparison of codes NIPS in group I.

Parameters	NIPS	EMLA (n=20)	Amethocaine (n=20)	4% lignocaine (n=19),
		N (%)	N (%)	N (%)
Prior to cannulation	Relaxed	06 (30)	11 (55)	06 (31.5)
	Mild pain	14 (70)	09 (45)	12 (63.2)
	Moderate pain	0	0	01 (5.3)
Immediate after cannulation	Relaxed	0	02 (10)	0
	Mild pain	16 (80)	18 (90)	13 (68.5)
	Moderate pain	4 (20)	0	06 (31.5)
After 3 minutes of cannulation	Relaxed	03 (15)	03 (15)	01 (5.3)
	Mild pain	17 (85)	16 (80)	17 (89.4)
	Moderate pain	0	01 (5)	01 (5.3)

Table 3: Mean±SD comparison of NIPS in group I.

NIPS	EMLA (n=20)	Amethocaine (n=20)	4% lignocaine (n=19)	P value
Prior to cannulation	0.60±0.750	0.75±0.55	0.89±0.74	0.359
Immediate after cannulation	3.85±0.58	3.25±0.64	4.21±0.78	0.001
After 3 minutes of cannulation	1.05±0.61	0.95±1.05	1.21±0.54	0.332
P value	0.001	0.001	0.001	-

Table 4: Comparison of FLACC in group II.

FLACC	EMLA (n=14)	Amethocaine (n=13)	Lignocaine (n=13)
Prior to cannulation			
Relaxed	0	01 (7.1)	0
Mild pain	13 (100)	13 (92.9)	13 (100)
Immediate after cannulation			
Mild pain	11 (84.6)	13 (92.9)	09 (69.2)
Moderate pain	02 (15.4)	01 (7.1)	04 (30.8)
After 03 minutes of cannulation			
Mild pain	13 (100)	14 (100)	13 (100)

Table 5: Mean±SD comparison of FLACC in group II.

FLACC	EMLA (n=20)	Amethocaine (n=20)	4% lignocaine (n=19)	P value
Prior to cannulation	1.93±0.83	2.38±0.65	2.00±0.71	0.241
Immediate after cannulation	5.62±0.76	5.21±0.97	6.31±0.75	0.012*
After 3 minutes of cannulation	1.71±0.47	1.54±0.66	2.0±0.58	0.120
P value	0.001*	0.001*	0.001*	

When compared between the three groups prior to cannulation, when compared between the three groups prior to cannulation**,** majority of the patients in three groups were having mild pain. One patient in amethocaine group was relaxed when compared to none in EMLA and 4% lignocaine group. When assessed between the groups, majority of the patients were in mild pain. It was higher in amethocaine group (92.9%) followed by EMLA (84.6%) and 4% lignocaine (69.2%). However, when checked for moderate pain, it was least in amethocaine followed by EMLA and lignocaine group. All the patients in three groups had mild pain after three minutes of cannulation. Statistically significant difference was observed only for immediate after cannulation

between the groups. However, when checked within a group, it was significant for EMLA, amethocaine and 4% lignocaine. Amethocaine was more effective in alleviating pain immediately after venous cannulation (5.21±0.97) and three minutes post cannulation (1.54±0.66) compared to EMLA and 4% lignocaine as evident by lower mean±SD for the group. No statistically significant difference was observed for adverse effects. Two neonates (10%) in EMLA group and three neonates (15%) in amethocaine group had blanching in group one. One child (7.7%) in EMLA group and one child (7.1%) in amethocaine group had blanching in group two.

Table 6: Adverse effects.

Adverse effects	EMLA	Amethocaine	4% lignocaine	P value
Group I				
No side effects	18 (90)	17 (85)	19 (100)	
Blanching	02 (10)	03 (15)	0	0.353
Total	20 (100)	20 (100)	19 (100)	
Group II				
No side effects	12 (92.3)	13 (92.9)	13 (100)	
Blanching	01 (7.7)	01 (7.1)	0	1.00
Total	13 (100)	14 (100)	13 (100)	

DISCUSSION

The present study was done to study the comparison between EMLA, amethocaine and 4% lignocaine in alleviating pain during venous cannulation in children up to three year. In our study, the study population was divided into two groups. The first group included neonates in whom NIPS was used. Mean age of study population was of (0.35±0.14) months in group one. The mean age for EMLA, amethocaine and 4% lignocaine in group one was (0.35±0.13) months, (0.35±0.15) months and (0.35±0.15) months respectively which was demographically. Comparable without any significant difference. Mean weight of study population for group one was (3.03±0.43) kg. The mean weight for EMLA, amethocaine and 4% lignocaine in group one was (2.99±0.41) kg, (3.02±0.41) kg and (3.09±0.48) kg respectively which was demographically comparable without any significant difference. The male:female ratio was 35:24 for group 1. In group one male:female ratio in EMLA, amethocaine and 4% lignocaine group were 9:11, 2:3 and 7:12 respectively. Female predominance was seen in group one and also in all the three subgroups in group one. Depending upon the response to painful stimulus during venous cannulation each case in group one with subgroup were divided into relaxed, mild, moderate and severe pain. In our study, amethocaine was more effective in alleviating pain immediately after cannulation (3.25±0.64) and three minutes post cannulation (0.95±1.05) compared to EMLA and 4% lignocaine as evident by lower mean±SD for the group. Mild pain was experienced by 90 % of the patient in Amethocaine, 80% of the patient in EMLA and 68.5 of the patients in 4% Lignocaine group. Moderate pain was observed in none of the patient receiving Amethocaine, 20% of the patient in EMLA group and 31.5% of the patient in 4% lignocaine group. The POST HOC test was used for overall comparison of analgesia between three groups. When checked for NIPS scores between two groups prior to cannulation, no statistically significant difference was observed between the groups. When checked for NIPS scores between two groups immediately after cannulation, statistically significant difference was observed between EMLA and 4% lignocaine and between amethocaine and 4% lignocaine but not between EMLA and amethocaine. The key finding of this study is that the mean pain score of the patients of 4% lignocaine was significantly higher than that of the patients receiving EMLA and amethocaine ($p<0.001$) which suggested that EMLA and amethocaine offer better pain relief than 4% lignocaine under similar condition but however the difference between EMLA and amethocaine was not statistically significant. As Molodecka et al in their study concluded that neither speed of onset nor quality of anesthesia produced by amethocaine formulation was superior to that produced by EMLA.[3] Comparative costing analyses of the dermal anesthetic agents identify Amethocaine cream to be costlier than lignocaine-prilocaine cream. Our finding was similar to study conducted by Choy et al which concluded that there was no significant difference between EMLA and Amethocaine in relieving the pain and distress of needle puncture in children.[6]

But the following study results are not concordant with our study. In a study of Browne et al the VAS score for Amethocaine gel were lower than for EMLA ($p=0.0002$).[7] Romsing et al compared EMLA cream with Amethocaine gel applied under similar conditions and concluded that Amethocaine gel was significantly better than EMLA cream in reducing the pain of i.v. cannulation.[8] It was seen in the previous study by McCafferty et al that Amethocaine formulation provided superior quality of percutaneous anesthesia when compared with EMLA cream.[9] A Cochrane review examining efficacy of Amethocaine gel and EMLA cream for pain relief during cannulation in children found Amethocaine to be superior as analgesic. In a study by

Taddio et al Amethocaine was found to be more efficacious than EMLA when both anesthetics were applied for the same amount of time.[10] Most common adverse effect following EMLA application are blanching, erythema as well as methemoglobinimea. There is a risk of possible development of methemoglobinemia from the prilocaine metabolite o-toluidine during EMLA metabolism. Amethocaine application have been reported with side effects like severe burning, stinging, swelling, oozing, blistering, nausea, vomiting and irregular heartbeats. Adverse effect following topical lignocaine are severe burning, stinging, swelling, redness and dizziness. Two neonates (10%) in EMLA group and three neonates (15%) in Amethocaine group had blanching in group one. In our study adverse effect was seen in very few patients which was statistically insignificant which was concordant with following studies. In the study by Arendt's et al, One patient with 4% Amethocaine gel developed blistering and other adverse effects like erythema, wheal and pruritus were also reported.[11] In the study by Sawyer et al, Amethocaine patch produced significantly more erythema than did lignocaine-prilocaine cream.[12] The second group included children between two months to three years of age in whom FLACC was used. Mean age of study population was of 14 months for group two (14.17±7.22) months and were comparable. The mean age for EMLA, Amethocaine and 4% Lignocaine in group two was (15.00±6.94) months, (13.92±7.19) months and (13.54±8.03) months respectively. Mean weight of study population for group two was (3.03±0.43) kg and were comparable. The mean weight for EMLA, Amethocaine and 4% Lignocaine in group two was (9.82±2.57) kg, (9.27±2.77) kg and (8.80±3.00) kg respectively. The male: female ratio was 35:24 for group one. In group two male: female ratio in EMLA, Amethocaine and 4% Lignocaine were 3:4, 3:10 and 7:6 respectively. Group two had male predominance as evident by male: female ratio being 35:24. Amethocaine was more effective in alleviating pain immediately after cannulation (5.21±0.97) compared to EMLA and 4% lignocaine as evident by lower mean +_SD for the group. Mild pain was experienced by 92.6% of the patient in Amethocaine, 84.6% of the patient in EMLA and 69.2% of the patient in 4% Lignocaine group. Moderate pain was observed in 7.1% of the patient receiving Amethocaine, 15.4 % of the patient in EMLA group and 30.8 % of the patient in 4% lignocaine group. The post hoc test was used to test the difference between the groups. When checked for FLACC scores between two groups prior to cannulation, no statistically significant difference was observed between EMLA and Amethocaine, EMLA and 4% Lignocaine and Amethocaine and 4% Lignocaine. When checked for FLACC scores between two groups prior to cannulation, no statistically significant difference was observed between EMLA and Amethocaine while it was significant between Amethocaine and 4% Lignocaine and Amethocaine and 4% Lignocaine. When checked for FLACC scores between two groups prior to cannulation, no statistically significant difference was observed between EMLA and Amethocaine, Amethocaine and 4% Lignocaine and EMLA and 4% Lignocaine. Amethocaine had better analgesic effect compared to EMLA and 4% Lignocaine as evident by lower mean±SD for the group, but however the difference between Amethocaine and EMLA was statistically insignificant. One child (7.7%) in EMLA group and one child (7.1%) in Amethocaine group had blanching which was statistically insignificant.

Limitations

Limitations of current study were, the sample size was small due to COVID pandemic. FLACC score has lower validity compared to MBPS. All the three drugs had same application time and was used in similar quantity.

CONCLUSION

In current study, amethocaine significantly reduces the pain response as compared to EMLA and 4% Lignocaine group specifically immediately after cannulation and three minutes post cannulation. So, result of our study concluded that amethocaine is an efficacious agent in reducing acute pain in children in procedures such as venous cannulation. Further studies with large sample size, different application time, and different age group are required because effect of EMLA, amethocaine and 4% Lignocaine may differ with weight, age, presence of amount of subcutaneous fat, and application time. Other methods of pain assessment (Wong-Baker faces pain scale, visual analogue, CRIES scale) should also be used apart from NIPS and FLACC).

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Sharma R, Kumar P, Sood A, Gupta S. Comparison of effect of EMLA, amethocaine and 4% lignocaine in alleviating pain during venous cannulation in children up to three years. Int J Contemp Pediatr 2022;9:529-35.