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A COMPARATIVE STUDY OF INTRANASAL MIDAZOLAM SPRAY VERSUS EUTECTIC MIXTURE OF 2.5% LIDOCAINE AND 2.5% PRILOCAINE (EMLA) TO ATTENUATE PAIN OF PERIPHERAL VENOUS CANNULATION IN CHILDREN: A PROSPECTIVE RANDOMIZED CONTROL TRIAL.

Anaesthesiology

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ABSTRACT

Background: Eutectic mixture of local anesthetics (EMLA) (2.5% Lidocaine and 2.5% Prilocaine) cream is the commonly used topical anesthetic for painful intradermal procedures. Intranasal Midazolam spray has successfully been used to sedate patient for short duration. **Aims:** This study was conducted to compare effectiveness of Intranasal Midazolam spray and EMLA cream for intravenous (IV) cannulation in children. **Methods:** In this prospective single-blind randomized study, ninety-nine paediatric patients were assigned into Group A (number(n) =51) with Intranasal Midazolam spray applied before procedure and Group B (n = 48) EMLA cream applied 1 hour prior to cannulation. Vital signs were recorded before, during, and after the procedure. The primary objective of the study was assessment of severity of pain during IV cannulation using 10 cm visual analogue scale (VAS). Secondary objectives such as ease of cannulation and adverse effects were also noted. **Results:** All cannulation were performed in the first attempt with no adverse effects in both Midazolam group and EMLA group. The median (interquartile range) VAS score was 2 cm (1 to 3) in both the groups with a P value of 0.58. **Conclusion:** Intranasal Midazolam spray applied 2 minutes before venous cannulation is as effective as EMLA cream applied an hour before cannulation in children in providing dermal analgesia for intravenous cannulation with an added advantage of rapid onset of action in the former group.

KEYWORDS

EMLA cream, Midazolam nasal spray, topical, eutectic mixture, cannulation, analgesia, pain, children

INTRODUCTION

Peripheral intravenous cannula insertions are the two most common and painful procedures in hospitalized children in health care today.[1,2] Intravenous (IV) cannulation can be agonizing and traumatic for both the child, the parent, and the care provider. Fragile skin, small caliber and collapsed veins, anatomical variations, along with the child's apprehension, and withdrawal add to the complexity and difficulty of the anaesthesiologist. [3] Pain can trigger post-traumatic stress in children, making them unable to cooperate during anaesthetic induction. Minimizing pain and anxiety are not only imperative but also important for preventing long-term behavioral problems and adverse clinical outcomes.[4] So, we must actively and passionately participate as perioperative physicians in creating the most appropriate and comfortable environment for the child having surgery.

Pain relief for intravenous cannulation can be achieved in various ways, including pharmacologic and non-pharmacologic approaches. Topical anesthetic preparations such as the eutectic mixture of local anesthetics EMLA cream (2.5% Lignocaine and 2.5% Prilocaine), amethocaine cream, injection of local anesthetic, and nitrous oxide gas administration are among the pharmacologic techniques.[5] Distraction strategies, images, coping mechanisms, parental training, behavioral therapies, and music therapy are examples of non-pharmacological methods. The EMLA cream has been the standard of care in many pediatric institutions. This mixture's main drawbacks include an application time of 60-90 minutes before IV placement, venoconstriction, skin blanching leading to difficult IV cannulation, and risk of methemoglobinemia in children below 1 year of age. [3,6]

Studies conducted in the past have indicated that a Intranasal Midazolam spray can provide short term sedation and analgesia for venipuncture.[7] The Intranasal Midazolam spray provides several advantages, including a quick onset of effect, a painless convenient application method, easy availability, low cost, and a pleasant odor. Hence, this single-blind, randomized controlled trial in children was primarily designed to investigate the efficacy of Intranasal Midazolam spray versus EMLA cream in facilitating analgesia for venous cannulation using the visual analogue scale (VAS) pain score and also, with the secondary objectives of comparing the ease of cannulation and incidence of adverse effects if any in both the groups.

METHODS

This prospective, single centre, single blind, randomized controlled trial was conducted after approval from department dissertation and institutional ethics committee. Then, the trial was registered prospectively at the Clinical Trials Registry of India and conducted at tertiary care and referral center over a period of 2 months between March 2024 and April 2024.

In the study, ninety-nine children, belonging to American Society of Anesthesiologists (ASA) physical status (PS) I and II, aged 7-17 years undergoing elective surgical procedures requiring anaesthesia without any peripheral IV access were enrolled. Children with difficult IV cannulations, those undergoing emergency surgeries, with burns, broken, or infected skin and with intellectual disabilities were excluded.

All paediatric patients scheduled for surgery were evaluated on the previous day of surgery. The patients were assessed by observer 1 for suitability for inclusion in the study during preoperative evaluation. They were allocated into two study groups by a computer-generated table of random numbers using concealed opaque sealed envelope with prior informed consent from the parents and written assent from the participants.

In Group A (Intranasal Midazolam spray group), the children had an application of Intranasal Midazolam spray single time (5 mg) according to dose (0.2-0.5 mg / kg) 5 minutes before venous cannulation.

In Group B (EMLA cream group), the children had an application of an appropriate amount of EMLA cream for 60 minutes and the site was covered by a transparent occlusive dressing before venous cannulation. The children and their parents were explained in detail about the objectives, methodology, advantages, and likely complications of the study. Information on the reason for IV cannulation was given as per the child's age and developmental understanding. VAS was shown and explained to each patient during pre-anesthetic check-up a day prior to surgery and again re-explained prior to cannulation on the day of surgery to ensure adequate understanding by them. None of the patients enrolled in the study had difficulty in understanding the scale.

On the day of the surgery, the child along with the parent was shifted to the preoperative holding area. Standard monitors like non-invasive blood pressure, electrocardiogram, and pulse oximeter were attached

and vitals were recorded. Each participant was randomized to either Group A (Intranasal Midazolam spray) or Group B (EMLA cream) and the study drug was applied with the transparent occlusive dressing along with oxygen support by hudsons mask. Suitable and easily seen or palpable veins on the dorsum of non-dominant hand or forearm were preferred. The occlusive dressing was removed just before IV cannulation and the skin was wiped dry. At this point, the patient was asked to report if they felt any abnormal sensations like burning or stinging at the site of application. The blinding of the SS (observer two) was maintained by removing the topical anesthetic cream and dressing before he or she arrived to perform the IV cannulation. The choice of IV cannula (24 to 18 gauge) was dependent on the age, clinical condition, and perioperative requirements of the child.

Hemodynamic parameters like heart rate, blood pressure, and oxygen saturation were recorded 5 minutes before (baseline), at the time of cannulation, and 5 minutes after cannulation. The clinical utility of topical anesthetic asease of cannulation was graded on a 4-point scale as follows: grade 1-insertion at first attempt, grade 2-number of minor adjustments needed, grade 3-second attempt needed, and grade 4-more than two attempts needed.

Pain assessment was done by VAS of 0 (no pain) to 10 (unbearable pain) cm. Post-cannulation complications (erythema, edema, and induration) were assessed at 20, 40, and 60 minutes. Data analysis was done using statistical package for social sciences for Windows (version 22.0 released 2013. Armonk, New York: International Business Machines (IBM) Corporation) was used to perform statistical analysis. The sample size was calculated using the G Power v. 3.1.9.4 (Franz Faul, Universität Kiel, Germany) software.

The primary end point was the VAS pain score. A difference of 10 mm between the mean VAS pain scores of the groups was selected as the minimum clinically significant value.[8] Using this value, it was calculated that a sample size of 90 subjects was sufficient to detect an effect size of 0.4 for difference in mean VAS with a standard deviation of 1.05 in Group A (Intranasal Midazolam spray) and 1.12 in Group B (EMLA Cream) for pain scores between groups at a significance level of 0.05 (two sided) with 80% power. Estimating an approximately 10% loss to follow-up, we included a total of 99 subjects.

Descriptive analysis of all the explanatory and outcome parameters has been done using frequency and proportions for categorical variables, whereas mean and standard deviation was used for continuous variables. Mann-Whitney test was used to compare the mean age, body mass index levels and VAS scores between the 2 groups at different time intervals. Chi-square test was used to compare the gender and post-cannulation complications between the two study groups. Two-way repeated measure analysis of variance (ANOVA) was used to examine the changes in heart rate, systolic blood pressure, and diastolic blood pressure at three time points that comprised of before, during and after the procedure. The level of significance was set at $P < 0.05$.

RESULTS

A total of 99 eligible participants were included in the study between March 2024 and April 2024, with 51 and 48 participants in Groups A and B, respectively, with no loss to follow-up [Figure 1].

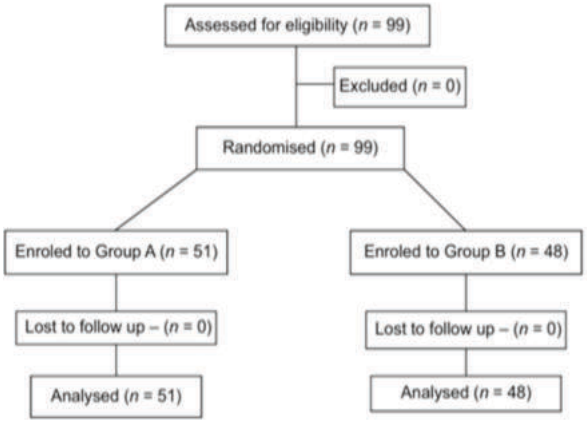

Figure 1: CONSORT Study flow chart

Demographic characteristics of participants were comparable in both the groups, suggesting that patient characteristics were unlikely to have influenced the study results [Table 1].

Table 1: Distribution Of Study Participants In The Two Groups According To Age, Gender And Body Mass Index.

Table 1: Distribution of study participants in the two groups according to age, gender, and body mass index			
Patient Characteristics	**Group A (*n*=51)**	**Group B (*n*=48)**	***P***
Age* (years)	12.22±3.0	12.5±2.9	0.653
Gender† (%)			
Male	60.8%	70.8%	0.642
Female	39.2%	29.2%	
Body mass index* (kg/m^2)	18.2±4.0	18.7±3.7	0.354

*Mann-Whitney test. †Chi-square test

All the peripheral venous cannulations were performed in the first attempt. The median VAS score was 2 cm (interquartile range (IQR) of 1 to 3 cm) in both the groups, P = 0.586 [Table 2].

Table 2: Comparison Of VAS (cm) Score Among The Two Groups.

Group	Number of subjects (*n*)	VAS score (cms) Median (Q1, Q3)	*P*
Group A	51	2 (1, 3)	0.586
Group B	48	2 (1, 3)	

The mean value of hemodynamic parameters during the baseline period (5 minutes before cannulation) and post-cannulation (5 minutes after cannulation) in both the groups were comparable. The vital parameters were on the lower side before the venous cannulation, while it increased during the procedure in all three parameters, namely heart rate, systolic blood pressure, and diastolic blood pressure [Figure 2].

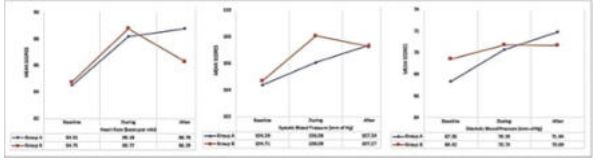

Figure 2: Heart Rate, Systolic And Diastolic Blood Pressure Of Study Participants In Both The Groups.

However, the heart rate and systolic BP increased in Group A after the procedure and decreased in Group B. The diastolic BP increased in Group A while remained unchanged in Group B, after the procedure. On application of repeated measures of ANOVA, it was noted that there was a statistically significant difference within the time points ($P < 0.05$) in all three vital parameters but it was not clinically significant.

In Group A, among a total of 51 participants, 46 participants were cannulated at the first attempt (90.2%), and 5 participants were cannulated with minor adjustments (9.8%). Whereas, in Group B, among a total of 48 participants, 44 participants were cannulated at the first attempt (91.6%) and 4 participants were cannulated with minor adjustments (8.4%). The difference was insignificant (P = 0.9) [Table 3].

Table 3: Comparison Of Ease Of Cannulation Between 2 Groups

Variable	Category	Group A		Group B		*P*
		n=51	%	*n*=48	%	
Ease of cannulation	Insertion at first attempt	46	90.2%	44	91.6%	0.951*
	Number of minor adjustments needed	5	9.8%	4	8.4%	

*Fisher's exact test

No post-cannulation complications such as the erythema, edema, and induration were observed at 20-minute, 40-minute, and 60-minute time intervals among both the groups.

DISCUSSION

Our study focused on the topical and intranasal analgesia for children aged between 7 and 17 years undergoing peripheral venous cannulation. The analgesic properties of Intranasal Midazolam spray were compared with that of EMLA cream by measuring the VAS scores. Various studies undertaken to co-relate the children's cognitive ability with their ability to use VAS have proven the conceptual ability of children of 7 years and above to accurately use VAS. The pain assessment on VAS with EMLA was comparable in terms of pain ratings as observed in previous studies.[9,10]

Our study revealed that the VAS scores between the two groups were

comparable, hence, the analgesic properties of Intranasal Midazolam spray for procedural analgesia were similar to that of EMLA cream. Few studies in the past have recommended that the Intranasal Midazolam spray is an effective anesthetic Intranasally. In a randomized, double-blind, placebo-controlled study, the investigators evaluated the analgesic efficacy of Intranasal Midazolam spray in 144 patients undergoing arterial blood gas sampling using the VAS. The VAS score was 1.5 (IQR: 2.0) for the Intranasal Midazolam group and 5 (IQR: 2.0) for the placebo group. The study concluded that Intranasal Midazolam spray had better analgesic effect compared to placebo because it affects free nerve endings associated with pain and heat.[11] In another randomized trial, the cutaneous anesthetic effect of 8% lignocaine spray against lignocaine patch was compared using a more objective assessment by the current perception threshold (CPT) test. In the study, thirteen healthy male participants were randomly assigned to one of three treatments: a metered-dose 8% lignocaine spray, a lignocaine patch, or no treatment which was behaving like a control. In both the groups, CPTs for 250 and 2000 Hz stimuli were considered greater at 30 minutes after administration than at baseline and were comparable. They concluded that, like the lignocaine patch, the lignocaine spray provided weak equivalent analgesia after 30 minutes of treatment. When compared to the lignocaine patch, the advantage of the lignocaine spray was speedier onset of action. As a result, the role of 10% lignocaine spray as a beneficial topical anesthetic for superficial unpleasant operations of mild to moderate pain intensity is established.[12]

In yet another randomized double-blind trial using topical xylocaine® 10% pump spray to enhance analgesia for venepuncture on 100 pregnant patients scheduled for caesarean section, the authors concluded that pre-treatment with topical xylocaine® pump spray was a more convenient and effective approach of minimizing venepuncture-related pain. In this study, the authors emphasize the fact that 10% xylocaine spray in high concentrations and presence of skin penetration enhancers such as polyethylene glycol and ethanol have the ability to penetrate the deeper layer of skin.[13] Similarly, a randomized controlled trial that evaluated the analgesic effects of 10% lignocaine spray versus placebo in 570 pregnant women undergoing amniocentesis reported that the median procedural pain score was significantly lower among the women who received lignocaine spray when compared to placebo. Since the procedure was of short duration, the analgesic effect of the drug was not well understood; but lignocaine spray has several advantages such as fast onset of action, non-invasive method of application and global availability. Hence, the lignocaine spray has got good acceptance for the provision of analgesia for short minimally invasive procedures.[14]

On the contrary, a randomized double blinded placebo-controlled trial comparing topical application of 60 mg of 10% lignocaine spray with a placebo (0.5% of chlorhexidine gluconate in 70% alcohol base) before IV cannulation in adults found that topical lignocaine spray was not effective in reducing pain during IV cannulation. The authors attributed the placebo effect to have played a major role in reducing the pain during IV cannulation among the participants. These results may not be comparable with children as transdermal uptake of topical lignocaine spray may vary between children and adults owing to factors such as optimal dose, duration, surface area of application, temperature, cutaneous vaso-activity, hydration of skin, and preoperative anxiety.[15] Although EMLA cream is a time-tested choice for relieving pain and discomfort associated with venous cannulation in children, recent studies have recommended other alternatives to EMLA due to many disadvantages associated with its use. EMLA has vasoconstrictive properties reducing the caliber of veins,[16,17] slower onset of action, increased risk of methemoglobinemia and is more expensive than other popular alternatives. EMLA is not recommended for use in children less than a month old.[18-20]

This study emphasizes the effectiveness of 10% lignocaine spray for procedural analgesia for IV cannulation in children. Each dose of spray in the study consisted of 0.1 ml solution equivalent to 10 mg. The researcher sprayed topical lignocaine spray 3 times amounting to 30 mg at the intended site of cannulation after disinfecting the site with isopropyl alcohol. This dose was chosen based on the research conducted by Van Straten et al. and Kanai et al.[12,13] In order to evaluate the effectiveness of topical spray in children, we conducted a pilot study in the age group of 7 to 17 years of age and found it to be effective in the dosage of 30 mg.

The physio-chemical properties of lignocaine facilitate rapid lipid membrane penetration and onset of cutaneous anesthesia once the sub-epidermal nerve endings have been reached.[12,21-23] Cutaneously applied lignocaine must first cross the relatively impermeable stratum corneum, a teleological defense barrier.[24] A recurring theme is facilitation of transfer of topical lignocaine across the stratum corneum.[25-29] Different mechanisms to enhance drug transfer across the stratum corneum include using a high drug concentration, addition of solvent vehicles or penetration enhancers (e.g. Water, ethanol, polyethylene glycol) or application of an occlusive dressing over the treated skin area.[24] Dermal application of high concentrations of lignocaine (8-10%) appears safe and serum levels were low even after application on broken skin. Owing to these desirable properties and safe profile, we chose to compare 10% lignocaine spray with EMLA cream which is the standard of care in paediatric population. However, further studies of optimal design and larger sample size need to be conducted to explore newer methods to alleviate pain during cannulation process.

We enrolled children aged 7 to 17 years; hence, the results may not be applicable to infants and toddlers in whom establishing IV access may be more challenging. Other limitations were that the role of preoperative anxiety in children undergoing peripheral venous cannulation which could have influenced pain perception was not assessed in the study. Besides, we did not assess the cutaneous vasodilatation which could have an impact on the ease of cannulation.

CONCLUSION

Intranasal Midazolam spray is equally effective as EMLA cream for dermal analgesia during IV cannulation in children. Intranasal Midazolam spray is likely to serve as a safe, quick and a useful alternative in attenuating peripheral venous cannulation pain in the paediatric population due to fast onset of action and non-invasive method of application. Financial support and sponsorship All drugs required in the study were provided at no cost.

Conflicts Of Interest

There are no conflicts of interest.

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