

Pain during venous cannulation: Double-blind, randomized clinical trial of analgesic effect between topical amethocaine and eutectic mixture of local anesthetic

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Abstract

Background: Venous cannulation is often a painful procedure for the patient. Eutectic mixture of local anesthetic (EMLA) is the commonest topical analgesic used but suffers from disadvantages such as slow onset and skin blanching, which may interfere with venous cannulation. Amethocaine is a newer topical analgesic which seems to be devoid of such problems.

Materials and Methods: This prospective randomized double-blind study compared the analgesic efficacy of EMLA with amethocaine during venous cannulation in adults. Eighty ASA I-II patients, aged 18–65 years, were recruited. The test drug was applied on the designated site of venous cannulation and covered with an occlusive dressing for at least 60 min prior to the procedure. Data collected included visual analogue score (VAS) during first attempt at venous cannulation, the ease and success rate at cannulation, and cutaneous changes at the application site.

Results: Mean and median VAS for the EMLA group were 27.9 ± 9.8 and 30 mm, respectively; while for the Amethocaine group were 19.1 ± 14.1 and 20 mm, respectively. Differences in VAS did not reach statistical significance. No statistically significant differences were observed in the ease and success rate at cannulation. Cutaneous changes in the form of local induration and erythema (three patients in the Amethocaine group) and blanching (eight patients in the EMLA group) were mild, localized, and required no further treatment. No patient developed severe allergic reactions.

Conclusion: Topical EMLA and amethocaine were comparable in terms of analgesic efficacy and ease of venous cannulation in adult patients.

Key words: Amethocaine, eutectic mixture of local anesthetic, venous cannulation

Introduction

Venous cannulation is often a painful procedure with the potential to cause significant anxiety, distress, and discomfort.^[1-3] Pain relief prior to venous cannulation using topical analgesics is a growing practice as healthcare providers strive for a pain-free and pleasant hospital stay for patients.

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Eutectic mixture of local anesthetic (EMLA) is the most widely used topical analgesic since the early 1980s.^[4] Each gram of EMLA contains 25 mg of lignocaine and 25 mg of prilocaine. It is formulated as an oil-in-water emulsion, yielding an 80% concentration in the oil droplets, which facilitates its skin penetration.^[5] Despite its proven efficacy, its use has been limited by a few problems.^[3,6,7] These include a long onset time of 60 min,^[4] a potential for complicated venous cannulation due to blanching of the skin, a duration of only 30–60 min, and risk of methemoglobinemia in children below 1 year of age.^[8]

Amethocaine is an ester local anesthetic which is more lipophilic than either lignocaine or prilocaine, facilitating its passage across the stratum corneum.^[9] 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.^[10] With a seemingly better tolerability profile,

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amethocaine has been shown to be more superior,^[3,6,7,11,12] if not just as efficacious^[10,13,14] as EMLA in reducing pain during venous cannulation, especially in children.

As most of the data available were on the pediatric population, we carried out this study to compare the analgesic efficacy of EMLA 5% versus amethocaine 4% cream for venous cannulation in adults. Our study hypothesis was that amethocaine was more superior to EMLA in reducing venous cannulation pain in the adult population. Our major outcome was pain as assessed by visual analogue score (VAS) during venous cannulation, while minor outcomes were ease of cannulation and cutaneous effects such as blanching, local induration, or erythema.

Materials and Methods

This prospective randomized double-blind clinical trial compared the analgesic effects of EMLA 5% and amethocaine 4% during venous cannulation. Eighty ASA I–II patients aged between 18 and 65 years were recruited following approval from the institution's Medical Research and Ethics Committee. Subjects receiving concurrent analgesics or with a history of allergy to local anesthetics were excluded. Also excluded were pregnant or breastfeeding women, diabetic patients with peripheral neuropathy, and patients with poorly visible veins. Patients who were recruited were given detailed explanation about the study and written informed consent was obtained. They were briefed on the use of VAS between 0 mm (no pain) to 100 mm (the worst pain imaginable) for pain assessment. The intended site for cannulation was examined to make sure the skin was intact and healthy.

No premedication was given to the patients on the day of surgery. Syringes containing 1 ml of either EMLA 5% or amethocaine 4% were prepared and sealed in envelopes. Randomization was done by an assistant by means of coin toss. The test drug was applied on the dorsum of the patient's hand to form a 2-cm diameter circle and covered with an occlusive dressing (Tegaderm[®], 3M) for at least 60 min prior to venous cannulation. The actual duration of drug application was recorded.

In the operating theatre, venous cannulation using an 18G cannula (Venofix[®], B.Braun) was performed by a blinded investigator who had at least 3 years anesthetic experience. The VAS at initial venous cannulation was noted. Ease of cannulation was scored using a four-point scale, ranging from insertion at first attempt (1), a number of minor adjustments needed (2), a second attempt required (3), or failure of 2 or more attempts (4).^[10] The number of attempts was limited to

three. Venous cannulation was deemed to have failed when it was unsuccessful at the designated site after three attempts. Subsequent cannulation was attempted at another site by a senior anesthetist following skin infiltration with 1–2 ml of lignocaine 2%.

The presence of cutaneous manifestations following application of test drugs, such as localized induration, erythema, blanching, or urticaria, was recorded. Allergic reactions, if any, were noted and treated with standard rescue measures.

Sample size estimation was based on the mean \pm standard deviation (SD) of a similar study performed by Browne, which showed a VAS score of 25.3 ± 16.6 after cannulation with EMLA.^[6] To detect a 20% change in VAS, with an alpha error of 0.05 and a power of 80%, we calculated that sample size should be at least 32 patients per group. Estimating an approximately 20% dropout rate, we included 39 patients in each group.

Results were analyzed using SPSS program version 12. The differences in patient's age and BMI were compared using Student's *t* test, while differences in gender, race, ease of cannulation, and cutaneous manifestations were analyzed using Fisher's Exact test. The differences in VAS were tested using the Mann-Whitney U test. A *P* value of <0.05 was considered to be statistically significant.

Results

Figure 1 summarizes the study trial. A total of eighty patients were recruited, of which 39 patients were in the EMLA group and 41 patients in the Amethocaine group. One patient in the EMLA group had to be withdrawn from the study as the patient was an undisclosed intravenous drug user, the history of

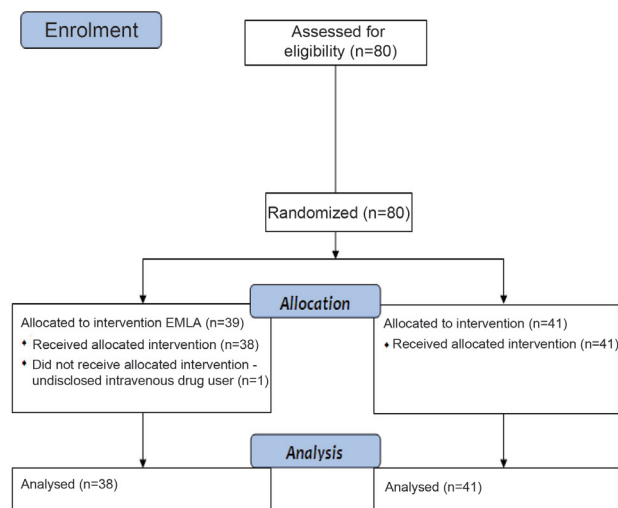


Figure 1: Summary of trial

Table 1: Patient characteristics and duration of application of test drug, expressed as mean \pm SD and numbers (percentage) where appropriate

	EMLA group (n = 38)	Amethocaine group (n = 41)
Age (years)	40.3 \pm 12.7	40.6 \pm 14.3
BMI (kg/m ²)	24.1 \pm 3.2	23.7 \pm 4.2
Gender		
Male	18 (47.4)	18 (43.9)
Female	20 (52.6)	23 (56.1)
Duration of application (min)	78.7 \pm 18.4	78.2 \pm 21.8

Student's *t* test used for age, BMI, duration of application; Fisher's Exact test for gender, EMLA: Eutectic mixture of local anesthetic

which was only revealed after the patient had been recruited. Patient characteristics are shown in Table 1. No significant differences were observed between the two groups in terms of demographic data and duration of application of test drug.

Mean VAS scores at initial venous cannulation, 27.9 \pm 9.8 mm (EMLA) and 19.1 \pm 14.1 mm (Amethocaine), showed no statistically significant difference ($P > 0.05$). The box-plot distribution of VAS [Figure 2] showed a greater dispersion in the Amethocaine group, while the distribution in the EMLA group was skewed to the left by the presence of an outlier (patient number 13) in the group. Median VAS for the EMLA group was higher at 30 mm compared to 20 mm for the Amethocaine group but this did not achieve statistical significance. The lowest VAS noted was zero in the Amethocaine group and 5 mm for the EMLA group. Maximum pain scores were 50 mm for both groups.

No significant difference in ease of cannulation was noted between the two groups. Cannulation was successful at the initial attempt in 35 patients (92.2%) in the EMLA group and 36 patients (87.8%) in the Amethocaine group. One patient from each group (2.6% from EMLA group and 2.4% from Amethocaine group) had failure of 2 or more attempts.

Local induration and erythema were noted in three patients (7.3%) in the Amethocaine group and mild blanching in eight patients (21.1%) in the EMLA group. No complications were noted in the rest of the patients. None of the patients developed any severe allergic reactions. Cutaneous changes were mild and localized. No treatment was required other than reassurance to the patients.

Discussion

The distress of needle puncture during venous cannulation or venepuncture is a particular problem in children and needle-phobic individuals. This is further influenced by age, anxiety,

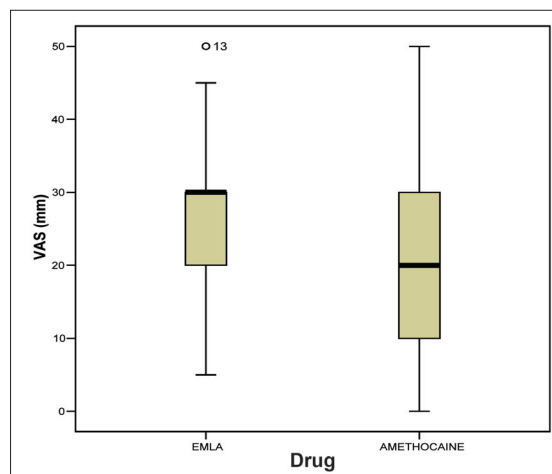


Figure 2: Comparison of pain score distribution Mann-Whitney U test used to compare VAS

and past experience, in which anticipatory anxiety correlated with high pain ratings.^[10] Thus, the alleviation of such pain and distress would be beneficial to all concerned.

Administration of topical anesthetics to control pain during venous cannulation avoids the use of local anesthetic infiltration, which may cause pain and obscure visibility of the vein. The ideal properties of a topical anesthetic should include ease of application, rapid onset of action, effective analgesia, long duration of action, minimal side effects, and suitability for use in all age groups.

The search for an ideal topical anesthetic over the years led to the development of EMLA in 1981.^[6] Since EMLA became commercially available in 1986, its use has expanded to include analgesia for arterial puncture,^[15] venepuncture,^[4,16] split skin grafts,^[17] removal of port wine stain,^[18] fistula cannulation,^[19] and many more procedures.^[4,5] The use of EMLA, however, is not without problems. The onset, depth, and duration of dermal analgesia on intact skin provided by EMLA depend primarily on the duration of application. To provide sufficient analgesia for venous cannulation and venepuncture, EMLA should be applied under an occlusive dressing for at least 1 h. To provide dermal analgesia for procedures such as split skin graft harvesting, EMLA should be applied for at least 2 h.^[17] This limitation, coupled with its relatively short duration of action of 30–60 min, often means that it is inconvenient and impractical in an operating theatre setting.

In contrast, amethocaine is an ester local anesthetic with desirable features such as comparatively longer duration of analgesia, greater potency, fewer side effects, and a faster onset of action of 30 min. However, its onset of action was not investigated in this study, as an application-to-cannulation interval of at least 60 min was necessary to double blind the

trial and to cater for the long onset time of EMLA. Many studies have reported amethocaine to be equal^[10,13,14] or superior^[3,7,11,12] to EMLA in terms of analgesic efficacy. The observed differences may be due to methodological variations in the dose of topical analgesic, surface area of application, or the size of intravenous cannula used. It should be noted that most of these studies were carried out on pediatric patients, possibly because pain and distress to the children and their families were thought to warrant more active intervention.

Unlike other studies,^[3,7,11,12] we failed to show significant differences in VAS between EMLA and amethocaine. As the mean and median VAS were less than 30 mm in both groups, it would appear both drugs were equally efficacious in providing analgesia for venous cannulation. There was a much greater dispersion for amethocaine compared to EMLA, implying heterogeneity in the patient response to venous cannulation following amethocaine. The distribution for EMLA group was skewed to the left due to the presence of an outlier. This could have affected the accuracy of our findings.

The findings in this study may be influenced by several factors. First, the recommended storage temperature for amethocaine 4% gel is 2–8°C even though it may be stored up to a month at 25°C at the point of use,^[10] while EMLA should be stored at 25°C or less.^[5] Temperature maintenance is vital during transport or storage and any increase in temperature above those stated might reduce its efficacy and affect the outcome of the study. Second, the VAS is a subjective scoring system which depends on the individual's perception and description of pain. A more objective assessment could include alterations in the patients' hemodynamic parameters in response to venous cannulation, which may be recorded and analyzed for correlation with pain scores. A third factor is the possible component of anxiety toward venous cannulation, which might influence pain perception and hence pain scores given by the patients. Our patients comprised mostly of day care surgery patients who did not receive premedication prior to anesthesia and surgery. In a study on venepuncture in children, Choy found that anticipatory anxiety of both parent and child were correlated with higher ratings of pain, emphasizing the fact that pain is not purely a sensory experience.^[10] However, Speirs investigated the anxiety and discomfort associated with venous cannulation in adults and found no significant relationship between the two.^[3]

In our study, the size of intravenous cannula was standardized to 18G to enable us to make a fair comparison. Our results were similar to the study done by Molodecka using 18G cannula, which showed no difference in the analgesic effect between EMLA and amethocaine.^[14] However, significant

differences were shown in many other studies using various sizes of cannula ranging from 20–22G^[3,9,11,16] to 16G.^[6] Arendts, on the other hand, did not specify the diameter of cannula used for cannulation and left this to the discretion of the person inserting it, as is usual clinical practice.^[20] The role of cannula size remains unclear, but it did not appear to play a significant part in affecting the outcome of our study.

The vascular response to cutaneous application of EMLA was investigated by Bjerring by means of skin reflectance spectroscopy and laser Doppler blood flowmetry.^[21] In healthy subjects, EMLA cream produced a biphasic vascular response with an initial vasoconstriction, maximal after 1.5 h of application. After prolonged application (>3 h), vasodilatation occurred, presumably because of a smooth muscle relaxant effect of the analgesics. In our study, eight patients were noted to have blanching of the skin while no erythema was noted. The biphasic vascular response was not seen in this study because the average time before cannulation was less than 2 h.

The vasoconstrictive effect of EMLA may potentially cause difficulty in intravenous cannulation, while the erythema effect of amethocaine can facilitate cannulation, as postulated by the Cochrane review on this subject.^[12] In our study, we noted that three patients receiving amethocaine developed redness and swelling, consistent with the documented side effect of amethocaine.^[9,10,17] We did not find significant difference in the ease of cannulation using amethocaine or EMLA or the number of attempts needed before successful cannulation. Similar results were also shown by Choy,^[10] Romsing,^[11] and Newbury^[22] during venous cannulation in children. The vasoactive effects of EMLA and amethocaine have minimal influence on the ease of cannulation.

The limitations to our study are two-fold. First, the most common method of analgesia for venous cannulation in our institution is by means of local infiltration of 1–2% lignocaine, rather than topical analgesia. The use of topical analgesia should ideally be compared to the standard analgesic technique to see whether there is justification to maintain status quo or adopt a new technique. Second, a placebo group with sham topical ointment would indicate whether topical analgesia is indeed indicated before venous cannulation. This was rejected as it is our institution protocol to provide analgesia prior to insertion of large-bore venous cannula (18G and above).

Conclusion

We studied topical EMLA and amethocaine in terms of analgesic efficacy and ease of venous cannulation in adult patients and found no significant differences in their

characteristics.

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