Topical amethocaine (Ametop™) is superior to EMLA for intravenous cannulation

John Browne FFARCSI,
Imad Awad MD,
Robert Plant FFARCSI,
John McAdoo FFARCSI,
George Shorten MD

Purpose: A eutectic mixture of local anesthetics (EMLA) is commonly used to provide topical anesthesia for intravenous (*iv*) cannulation. One of its side effects is vasoconstriction, which may render cannulation more difficult. A gel formulation of amethocaine (Ametop™) is now commercially available. The aim of this study was to compare EMLA and Ametop™ with regard to the degree of topical anesthesia afforded, the incidence of vasoconstriction and the ease of *iv* cannulation.

Methods: Thirty two ASA I adult volunteers had a # 16 gauge *iv* cannula inserted on two separate occasions using EMLA and Ametop™ applied in a double blind fashion for topical anesthesia. Parameters that were recorded after each cannulation included visual analogue pain scores (VAPS), the presence of vasoconstriction and the ease of cannulation, graded as: 1 = easy, 2 = moderately difficult, 3 = difficult and 4 = failed.

Results: The mean VAPS ± SD after cannulation with Ametop™M was 12 ± 9.9 and with EMLA was 25.3 ± 16.6 ($P = 0.002$). Vasoconstriction occurred after EMLA application on 17 occasions and twice after Ametop™ ($P = 0.001$). The grade of difficulty of cannulation was 1.44 ± 0.88 following EMLA and 1.06 ± 0.25 with Ametop™ ($P = 0.023$).

Conclusions: Intravenous cannulation was less painful following application of Ametop™ than EMLA. In addition, Ametop™ caused less vasoconstriction and facilitated easier cannulation. Its use as a topical anesthetic agent is recommended, especially when *iv* access may be problematic.

Objectif : Un mélange eutectique d'anesthésiques locaux (MEAL) est souvent utilisé pour l'anesthésie topique lors d'une canulation intraveineuse (*iv*). La vasoconstriction, qui est l'un des effets secondaires du MEAL, peut compliquer la mise en place d'une canule. Une présentation en gel d'améthocaïne (Ametop™) est maintenant offerte dans le commerce. Le but de la présente étude était de comparer le MEAL et l'Ametop™ en regard du degré d'anesthésie topique fourni, de l'incidence de la vasoconstriction et de la facilité de la canulation *iv*.

Méthode : On a inséré, en deux occasions séparées chez 32 volontaires adultes d'état physique ASA I, une canule *iv* de calibre 16 en utilisant en double aveugle le MEAL et Ametop™ pour réaliser l'anesthésie topique. Après chaque canulation, on a enregistré les paramètres suivants : les scores de douleur à l'échelle visuelle analogue (EVA), la présence de vasoconstriction et la facilité de canulation notée 1 = facile, 2 = modérément difficile, 3 = difficile et 4 = impossible.

Résultats : Les scores moyens à l'EVA ± l'écart type ont été de 12 ± 9,9 à la suite de la canulation avec Ametop™M et de 25,3 ± 16,6 après le MEAL ($P = 0,002$). La vasoconstriction est survenue en 17 occasions après l'application du MEAL et deux fois plus souvent après Ametop™ ($P = 0,001$). Le degré de difficulté de canulation a été de 1,44 ± 0,88 après le MEAL et de 1,06 ± 0,25 après Ametop™ ($P = 0,023$).

Conclusion : La canulation intraveineuse est moins douloureuse après l'application d'Ametop™ que celle du MEAL. De plus, l'Ametop™ a provoqué moins de vasoconstriction et a facilité l'introduction d'une canule. Son usage comme anesthésique topique est recommandé, surtout lorsqu'une action rapide est nécessaire ou que l'accès *iv* peut être problématique.

From the Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital and University College Cork, Wilton, Cork, Ireland.

Address correspondence to: Professor George Shorten. Phone: 353-21-546400, Ext. 2490; Fax: 353-21-546434; E-mail: shorteng@shb.ie

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THE pain associated with intravenous (*iv*) cannulation is an important problem which confronts anesthesiologists daily. Undesirable sequelae include anxiety, tachycardia and hypertension.[1] Several formulations of local anesthetics have been developed in an attempt to provide effective analgesia of intact skin by topical application. A eutectic mixture of local anesthetics (EMLA) contains lidocaine 2.5%, prilocaine 2.5%, arlatone (emulsifier), carbopol (thickener) distilled water and sodium hydroxide.[2,3] Since its development in 1981, it has been demonstrated to be an effective topical agent for *iv* cannulation[4,5] provided it is applied as a thick layer[6] at least one hour before venepuncture and held *in situ* with an occlusive dressing. Serious side-effects are very rare but blanching of the skin and vasocontriction occur frequently.[7-9] Vasoconstriction may render *iv* cannulation more difficult.[10]

Ametop™ (Smith and Nephew) is a topical anesthetic gel containing amethocaine 4%, Xantan gum, methyl and propyl-p hydroxybenzoate, water and saline. Its manufacturers recommend that it is applied for 30-45 min, secured in position with an occlusive dressing and advise that side effects may include erythema, edema, and pruritus.

A prospective, randomised, double blind trial was carried to compare EMLA and Ametop™ with regard to the degree of topical anesthesia afforded, the incidence of vasoconstriction, the subsequent ease of *iv* cannulation and the incidence of side-effects.

Materials and methods

With institutional ethical approval and having obtained written informed consent, 36 ASA I adult (> 18 yr) volunteers were studied. Subjects receiving concurrent analgesics or with a history of allergy to local anesthetics were excluded.

Each volunteer underwent *iv* cannulation with a 16 gauge *iv* cannula (Insythe®, B.D) on two different occasions, one following the application of EMLA and the other following Ametop™ application. Random allocation determined whether EMLA or Ametop application was performed first.

For each cannulation, the selected topical anesthetic was applied thickly i.e. 2.5 g EMLA (from a 5 g tube) and 1.5 g Ametop™ (from a 1.5 g tube) over a 30 mm × 30 mm skin area. For both preparations application was performed one hour before cannulation and each was covered with an occlusive dressing (Tegaderm™, 3m). After 60 min, the dressing and excess cream were removed and the skin was inspected for erythema, blanching, urticaria, edema and vasoconstriction (determined visually as narrowing of the proposed vein for cannulation). The presence of pruritus was noted. The skin was cleansed with an alcohol swab and a 16 gauge *iv* cannula was inserted. The discomfort caused by the cannulation was immediately assessed using a 100 mm visual analogue pain score (VAPS). Difficulty of *iv* insertion was graded using a four point scale i.e. grade 1 = easy; grade 2 = moderately difficult; grade 3 = difficult and grade 4 = failed.

Two weeks later, the procedure was repeated in each subject on the contralateral arm using the second topical anesthetic preparation. The site of cannulation was typically the dorsum of the hand or forearm. A corresponding site on the contralateral arm was used.

The subjects and the investigator making the assessments were unaware of which topical anesthetic was being used. One of two experienced anesthesiologists inserted the cannulae (and made recordings). No subject had *iv* cannulae inserted by different investigators.

Statistical analysis of the differences in VAPS and the grade of difficulty of *iv* insertion was performed using two-tailed paired Student t test while differences in the frequency of occurrence of vasoconstriction and erythema were analysed using Fisher's Exact test. $P < 0.05$ was considered significant.

Results

The results are summarised in the Table. Thirty-six volunteers (19 male, 17 female) were recruited for the trial, of whom four were lost to follow-up before the second cannulation was performed. The data from 32 (18 male, 14 female) were analysed. Mean age was 28.3 yr with a range of 20 to 46 yr.

The VAPS for Ametop™ were lower than for EMLA (12.0 ± 9.9 *vs* 25.3 ± 16.6, $P = 0.0002$). Vasoconstriction occurred less frequently with Ametop™ than with EMLA (2/32 compared with 17/32, $P = 0.001$). Ametop™ was associated with easier *iv* cannulation than EMLA (mean grade of difficulty, 1.06 ± 0.25 *vs* 1.44 ± 0.88, $P = 0.023$). Blanching occurred more frequently with EMLA

TABLE Data representing the mean ± SD and frequency of occurrence. *$P < 0.05$. VAPS - Visual Analogue Pain Score (mm).

	EMLA (n = 32)	*Ametop (n = 32)*
VAPS (mm)	25.3 ± 16.6	12.0 ± 9.9*
Cannula insertion grade of difficulty	1.44 ± 0.88	1.06 ± 0.25*
Vasoconstriction	17	2*
Blanching	23	2*
Erythema	2	11*
Edema	0	0
Urticaria	0	0
Pruritus	0	2

(23/32 *vs* 2/32, $P < 0.001$) while erythema was observed more often with Ametop™ (11/32 *vs* 2/32, $P < 0.05$). Mild transient pruritus was reported in two subjects following Ametop™ application.

Discussion

The most important findings of this study are that after one hour application, Ametop™ provides superior topical anesthesia than EMLA for *iv* cannulation in adults and is associated with less difficulty in cannula insertion.

The ideal topical anesthetic preparation should contain sufficient concentration of the active agent, provide a rapid onset of action combined with a deep and relatively prolonged anesthesia of the skin and have minimal side effects. In 1981, it was discovered that, when mixed together the two crystalline bases of lidocaine and prilocaine become an oily fluid at room temperature as a result of the lowering of the respective boiling points.[2,3] The mixture provides approximately 80% active local anesthetic in each droplet compared with 20% if lidocaine alone was emulsified.[11] EMLA has been available commercially in the U.K. since 1986. Since its introduction it has been employed to provide topical anesthesia in venepuncture,[5] arterial[12] and A-V fistula cannulation,[13] harvesting of smaller split skin grafts,[14] lumbar puncture,[15] removal of molluscum contagiosum,[16] cautery of genital condylomata,[17] myringotomy,[18] post herpetic neuralgia[19] and retrobulbar injection.[20]

However, application of EMLA may be associated with adverse sequelae. Blanching and vasoconstriction occur commonly after it is applied for one hour. This effect lasts for one to two hours while, after longer application times of two to four hours, erythema of the skin may be observed.[8] It has been shown that vasoconstriction may be elicited by placebo cream under an occlusive dressing, suggesting that the occlusion and not the preparation is responsible.[8] However, it is likely that the blanching (and vasoconstriction) is determined by the anesthetic mixture in EMLA and not by the vehicle or the occlusion.[9,10] Vasoconstriction can cause difficulty with *iv* cannula insertion. This has been overcome with the addition of a glyceryl trinitrate 2% ointment which led to easier *iv* cannulation with no change in pain scores.[10]

The results of our study show that Ametop™ causes less vasoconstriction and facilitates *iv* insertion. While vasodilatory effects were not obvious, Ametop™ was associated with erythema in approximately one third of subjects. Various topical formulations of amethocaine have been shown to cause erythema.[21-23] This is probably the result of the intrinsic vasodilatory effects of amethocaine.[23] However one study using a 5% preparation reported no significant erythema.[24]

One hour was chosen as the application time for both EMLA and Ametop™. This complied with manufacturers recommendations i.e. at least one hour for EMLA and 30-45 min for Ametop™. Although Ametop™ was applied for longer than the minimum recommended time, we do not feel that this bestowed any advantage, since the manufacturers of EMLA claim that 60 min is adequate application time to ensure topical anesthesia for venepuncture. Using identical times was necessary to double blind the trial and a 60 min interval, we feel, mirrors clinical practice. After one hour, Ametop™ provided better topical anesthesia. The greater efficacy of an amethocaine preparation compared with that of EMLA has previously been explained in terms of lipophilicity and anesthetic potency.[21] Amethocaine, is considerably more lipophilic than lidocaine or prilocaine, suggesting that amethocaine should penetrate more easily and rapidly through lipophilic material such as the stratum corneum. The implication of this greater lipophilicity is that onset of effect is likely to be more rapid, although the current study did not address this question. As amethocaine is also considerably more potent that either of EMLA's constituents, it is likely that it produces satisfactory anesthesia more easily having penetrated the stratum corneum. While some amethocaine formulations have illustrated this improved efficacy[22,23] others have failed to show any benefit over EMLA.[24] Compared with the latter study, by Molodecka *et al.*,[24] patients in our study received a greater dose of amethocaine (1.5 g *vs* 1 g) applied over a smaller area (3cm^2 *vs* 6 cm^2) and were subjected to a (presumably) more painful stimulus (16 G *vs* 18 G cannula insertion). These differences may account for the different findings of the two studies.

The absence of serious side effects in our study, while comprising just 32 volunteers, is consistent with the previously reported safety profiles of EMLA and various amethocaine formulations. Following application of EMLA one case of methemoglobinaemia was reported in an infant.[25] Contact dermatitis has been documented with lidocaine[26] and mild rashes recorded with EMLA.[5,8] However, when application instructions are adhered to, toxic plasma concentrations of local anesthetics do not occur.[27] Several topical amethocaine preparations have not produced toxic manifestations,[21-23,28] although amethocaine has been noted in the past for its toxicity.[29-31] Amethocaine is an aminoester which is hydrolysed rapidly by cholinesterase enzymes, and thus has a short half-life. A combination of drug retention in and slow release

from the stratum corneum probably accounts for the lack of systemic toxicity of topical amethocaine formulations[21] and it has been demonstrated that the topical application of the maximum recommended dose, 100 mg, produced neither toxic plasma concentrations nor clinical evidence of toxicity.[32]

In conclusion, our results support the topical application of Ametop™ to facilitate *iv* cannulation, especially when vasoconstriction may be problematic or when time constraints do not permit prolonged application.

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