Reports of Investigation

EMLA[®] patch for intravenous cannulation in adult surgical outpatients

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Purpose: The purpose of this study was to evaluate the effectiveness of a single-unit-dose package of the EMLA[®] Patch for dermal analgesia during intravenous cannulation in adult outpatients and in preventing vaso-vagal side effects.

Methods: After giving consent, 51 ASA I-III adult outpatients participated in a randomized, double-blind, placebo-controlled, parallel-group trial to receive either an EMLA[®] or placebo patch applied to the intravenous cannula site for 60 to 90 min. Following cannula insertion, patients and investigators rated the pain using a 100 mm VAS ruler. The incidence and severity of vaso-vagal responses, local skin reactions, and willingness to pay for the patch were also evaluated.

Results: The median VAS pain score by patient assessment in the EMLA[®] patch group was lower (8 mm; range: 0-92) than in the placebo group (25 mm; range: 0-98, $P < 0.05$). The median VAS pain score by investigator assessment was also lower in the EMLA[®] patch group (15 mm; range 1-79) than in the placebo group (23 mm; range 3-81, $P < 0.05$). There was a notable difference in the number of vaso-vagal reactions (17 placebo vs 4 EMLA[®], $P < 0.05$). Eighty-eight percent of patients who received the EMLA[®] patch would be willing to pay for the patch in the future compared with 69% of the placebo patch patients.

Conclusion: This study showed that the EMLA[®] patch, applied for 60-90 min before venous cannulation reduced the pain of venepuncture and vaso-vagal side effects in adult outpatients.

Objectif : Évaluer pour la canulation veineuse l'efficacité analgésique du timbre cutané EMLA[®] chez des patients ambulatoires adultes et sa capacité de prévenir les réactions vasovagales secondaires.

Méthodes : Cinquante et un adultes consentants ont participé à cette étude aléatoire, à double insu, contrôlée avec placebo et en groupes parallèles. Un timbre EMLA[®] ou placebo a été appliqué au site de la canulation pendant 60 à 90 min. Après l'insertion de la canule, les patients et les investigateurs ont évalué la douleur sur une ÉVA de 100 mm. L'incidence et la gravité des réactions vasovagales, les réactions cutanées locales, l'acceptation des frais occasionnés par le timbre ont été évalués.

Résultats : La médiane du score sur l'ÉVA telle qu'évaluée par le patient dans le groupe EMLA[®] était inférieure (8 mm ; écart 0-92) à celle du groupe placebo (25 mm ; écart 0-98, $P < 0,05$). La médiane du score sur l'ÉVA telle qu'évaluée par l'investigateur aussi était inférieure dans le groupe EMLA (15 mm ; écart 1-79). Les réactions vasovagales sont aussi survenues moins souvent dans le groupe EMLA (17 vs 4), $P < 0,05$. À l'avenir, 88% des patients du groupe EMLA se sont dits prêts à payer pour le timbre comparativement à 69% du groupe placebo.

Conclusion : Cette étude montre que le timbre EMLA[®] appliqué 60 à 90 min avant la canulation veineuse diminue la douleur de la ponction veineuse et les effets vasovagaux secondaires chez des patients ambulatoires adultes.

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VENOUS cannulation is the most commonly performed invasive procedure in hospital patients.¹ It is painful and associated with a high incidence of vaso-vagal reactions and pressor responses in adult outpatients,^{2,3} Since most adult outpatients require venous cannulation immediately before surgery, they would expect the availability of an effective and non-invasive local anaesthetic to reduce pain and, possibly, the adverse effects of cannulation.

EMLA[®] is a topical anaesthetic cream composed of an eutectic mixture of two local anaesthetics (lidocaine and prilocaine). When applied topically under occlusion it provides effective dermal analgesia for venepuncture and its use in paediatric patients is now almost routine.⁴ To increase the ease and efficiency of EMLA[®] application, a single-unit dose package of EMLA[®], the EMLA[®] patch, has been developed. The patch is impregnated with one gram of EMLA[®] 5% emulsion. The EMLA[®] patch has been shown to reduce the pain of venepuncture in children.^{5,6} However, there is no information on the use of the EMLA[®] patch in adult surgical outpatients.

The primary objective of this study was to compare the EMLA[®] patch with a placebo patch for reduction of venepuncture pain and vaso-vagal side effects in adult outpatients. Secondary objectives were to evaluate: 1) the feasibility of using the EMLA[®] patch in an adult surgical outpatient facility, 2) the patient's willingness to pay for the EMLA[®] patch, and 3) the incidence of local reactions and safety with the EMLA[®] patch.

Method

The study was a randomised, double-blind, placebo-controlled, parallel-group trial conducted at a single centre. After approval from The University of British Columbia Clinical Screening Committee for Research and Other Studies Involving Human Subjects, 51 ASA I-III, adult surgical outpatients gave consent and were studied. Inclusion criteria were: outpatient surgery requiring preoperative venous cannulation, age ≥ 18 yr and sufficient understanding of the visual analogue pain scale (VAS). Exclusion criteria were: Previous use of EMLA[®] for *iv* cannulation, allergy or sensitivity to amide local anaesthetics, use of a sedative or analgesic drug 12 hr before venous cannulation, participation in a clinical trial in the previous two weeks, and active dermatitis or open wound at the patch application site.

Patients were randomized to receive either EMLA[®] or a placebo patch with equal probability and the randomization list was prepared in blocks of four with no stratification. The investigators and patients were

blinded to randomization. The EMLA[®] patch is a circle-shaped matrix saturated with one gram of a 5% eutectic emulsion of lidocaine (25 mg·g⁻¹ of emulsion) and prilocaine (25 mg·g⁻¹). An adhesive ring surrounds the matrix, measuring 9.6 cm,² and is used to attach the matrix to the middle of a square shaped adhesive dressing measuring 39 cm.² Foam medical tape was used as the adhesive. The placebo patch was visually identical to the EMLA[®] patch and was saturated with one gram of placebo emulsion that did not contain the active local anaesthetic ingredients.

The patch was applied to the dorsum of the hand (site of intravenous cannulation) once the patient had completed the admission protocol for the outpatient facility. Each patient received one treatment. Following the application, the patient waited in the preoperative lounge for 60–90 min. Before patch removal, local skin sensations (itching, burning, tingling and feeling cold) were assessed by the patient on a four-point verbal rating scale (VRS): 0=none, 1=mild, 2=moderate, and 3=severe symptoms. Following patch removal, the investigators assessed the following local reactions (oedema, redness, pallor, itching and pilo-erection) using the same VRS. The time of application and the time of removal of the EMLA[®]/placebo patch were recorded. Once the patch was removed, the skin was prepared with chlorhexidine 0.5% in alcohol before insertion of the intravenous cannula. One of the investigators performed all venous cannula insertions. Immediately following the insertion of a 20 G cannula, the patient rated the pain of the procedure using a 100-mm VAS (Visual Analogue Scale) ruler anchored at 0 mm (no pain) and 100 mm (worst pain imaginable). Using the same scale, the investigator also assessed the patient's pain response to the cannula insertion. The investigator also rated the ease of cannula insertion according to the following scale: easier than usual, as usual, more difficult than usual. Blood pressure measurements were obtained before and at one minute intervals after cannulation for six minutes with an automatic sphygmomanometer. The patient and investigators assessed vaso-vagal reactions (i.e., feeling faint, dizzy, light-headed, sweaty, hot, cold, or nauseated) according to the following scale: 0=none, 1= mild, 2=moderate and 3= severe symptoms. After surgery, the patients were asked about their willingness to purchase the EMLA[®] patch for future intravenous cannulation. Specific prices were not discussed with the patients.

All data were entered into an Oracle[®] database and transferred into SAS[®] through the SAS[®] procedure PROC SQL. Differences in the VAS pain scores, and other numerical variables, were compared using the

Wilcoxon rank sum test. Categorical variables were analysed using the Fisher exact test. The main approach for analysis of efficacy was: All Patients Treated (APT) approach.

The standard deviation for the sample size calculation was determined from a previous study under similar conditions using EMLA® cream.⁷ This suggested a standard deviation of pain measures on the VAS scale of 30 mm. Pre-study calculations determined that 24 patients in each group would be needed to detect a mean difference of 25 mm in VAS pain scores, based on a power of 80% and an alpha of 0.05.

Results

A total of 51 patients were enrolled. Fifty patients were available for APT analysis. Reasons for study cancellation of three patients were: one patient had undergone a mastectomy on the side upon which blood pressure measurements were to be made. The patch had been applied for 45 min but since blood pressure measurements would be missing it was decided to discontinue this patient. The other two were discontinued because they required more than two attempts at cannulation.

There were no noticeable differences between the treatment groups in the baseline patient characteristics and duration of patch application (Table I). No patient had <50% patch adhesion. Two EMLA patients had 50% to 74% adhesion, nine patients (3 EMLA, 6 placebo) had 75% to 99% adhesion, and the remainder had 100% adhesion.

There were no differences between groups in the number of needle attempts and the ease of cannula insertion (Table II). The median VAS pain score by patients assessment in the EMLA® patch group was 8 (range: 0–92), while the median in the placebo group was 25 (range: 0–98), $P < 0.01$. The median difference between treatment groups was 17 mm for the patients' assessment of pain and 8 mm for the investi-

gator's assessment of pain (Table III). The 95% confidence interval for the median treatment difference was –19 to –1 mm for investigator's and, –27 to –5 mm for patients' assessment of pain.

There were differences in the total number (17 placebo *vs* 4 EMLA®) and severity of the vaso-vagal reactions when reported by the patients (Table IV) but no difference when reported by the investigator. There were no differences between the two groups

TABLE I Patient demographics

Characteristic	EMLA® Patch	Placebo Patch
Sex (M/F)	7/17	6/20
Age (yr)	34 ± 14	35 ± 11
Weight (kg)	67 ± 14	71 ± 21
Height (cm)	168 ± 8	167 ± 12
Patch time (min)	66 ± 7	69 ± 9

Mean ± SD

TABLE II Number of cannulation attempts and ease of insertion

	EMLA® Patch	Placebo Patch	Total
No. of Attempts			
1 or 2 attempts	23	25	48
>2 attempts	1	1	2
Ease of insertion			
Easier than usual	2	–	2
As usual	20	20	40
More difficult	2	6	8

TABLE III Pain assessment by patients and investigators (VAS scores, APT analysis)

Assessor	EMLA® Patch	Placebo Patch
Patients	8 (0–92)*	25 (0–98)
Investigators	15 (1–79)†	23 (3–81)

* $P < 0.01$

† $P < 0.05$

Median (range)

TABLE IV Vaso-vagal reactions* (Patients' assessment)

Reactions	EMLA			Placebo		
	None	Mild	Moderate	None	Mild	Moderate
Dizzy Spells	23	0	0	24	1	0
Feeling Cold	22	1	0	21	3	1
Hot Flushes	23	0	0	24	0	1
Light-Headed	22	1	0	22	1	2
Nausea	22	1	0	23	1	1
Sweating	23	0	0	21	2	2
Feeling faint	22	1	0	23	2	0

$P < 0.01$

*Data missing for two patients in the EMLA group.

regarding local reactions or sensations. A moderate pallor under the adhesive was reported in 15 patients in the EMLA® Patch group and in 10 patients in the placebo patch group (Table V).

Willingness to pay results found that of the 50 patients who received a patch, 39 (78%) would be willing to pay for the patch in the future. Eighty-eight per cent of the patients who received an EMLA® patch (21/24) were willing to pay in the future compared with 69% who received the placebo patch (18/26; $P = \text{NS}$).

Discussion

The primary objective of this study was to evaluate the analgesic effect of EMLA® patch compared with a placebo patch applied to adults before intravenous cannulation on the dorsum of the hand. Using the VAS pain as the primary outcome variable, a difference between treatment groups was found for both the patient and the investigators' assessment of pain, with lower pain scores seen in patients treated with EMLA® patch. The median treatment differences were lower for the investigators' assessment of pain than for the patients' assessment. The lower pain scores of the investigators may be the result of indirect pain assessments that were based on behavioural cues from the patient compared with pain assessments that were based on the sensation of pain felt directly by the patient during the cannulation procedure.

The P -value of less than 1% provides sufficient justification to reject the null hypothesis and accept the hypothesis of a treatment difference. The results of this study are consistent with the results of previous studies comparing EMLA® cream with those of a placebo when applied to the dorsum of the hand in adults for venepuncture⁷⁻⁹ and for intravenous cannulation procedures.¹⁰ In addition, EMLA® cream is effective for both venepuncture¹¹ and intravenous cannulation¹² in children. So far, the EMLA® patch has been shown to be as effective as EMLA® cream when used for venepuncture in children.^{5,6,13} This study shows that the EMLA® patch is more effective than placebo when used to alleviate the pain of intravenous cannulation in adult outpatients.

These results are valid and reliable because the study was of a double-blind, randomized design. The treatment groups were well balanced with respect to age, weight and sex. Most of the patients were Caucasians and thus ethnic origin was not a confounding variable of the efficacy results.

The EMLA® patch is saturated with one gram of a 5% eutectic mixture of lidocaine and prilocaine and is a more precise drug delivery system than EMLA® cream (2.5 g) applied to the same area of skin as cov-

TABLE V Local skin reactions (Investigators' assessment)

	EMLA® Patch		Placebo patch	
	Mild	Mod	Mild	Mod
Pallor	0	15	0	10
Pilo-erection	0	0	0	0
Pruritus	0	0	0	1
Redness	0	0	0	1
Oedema	0	0	0	0
Total	0	15	0	12
Local skin sensations (Patients' assessment)				
Burning	1	1	1	0
Cold Feeling	1	0	4	0
Pruritus	4	1	2	0
Tingling	1	0	1	1
Total	7	2	8	1

ered by the patch. In addition, the EMLA® patch eliminates the need for occlusive dressings such as Opsite[®] and Tegaderm[®] and may eliminate the possibility of inadequate effect when EMLA® cream is incorrectly applied.

Vaso-vagal reactions were collected as part of the efficacy measurements, since it is postulated that they occur in response to the pain of the procedure.² The number of vaso-vagal reactions rated by the patients in the EMLA® patch group was lower than with the placebo group (Table IV). Thus, the EMLA® patch may have a role in the prevention of such complications.

Another objective of this study was to decide whether the EMLA® patch could be used in an adult outpatient setting in view of the one hour application time. All patients scheduled for surgery in the Surgical Daycare Centre at Vancouver Hospital and Health Sciences Centre are instructed to arrive at least 90 min before surgery. As shown in Table I the mean application time in both groups was slightly >60 min. Thus, if the nurse applies an EMLA® patch soon after registration, optimal dermal anaesthesia will be achieved by the time the patient requires venous cannulation without prolonging the waiting time.¹⁴ In facilities where the waiting time is less than in our Surgical Daycare Centre application of the EMLA® patch may still be beneficial. It has been shown that EMLA cream applications as short as 15 or 30 min¹⁵ and even five minutes¹⁶ are more effective than placebos.

In this study, 88% (21/24) of patients who received the EMLA® patch would be willing to pay for the patch compared with 69% (18/26) in the placebo group. Overall, 78% (39/50) of the patients would be willing to pay for a patch for future venous cannulation. These data also suggest that institutions can

probably pass on the acquisition costs of the EMLA® patch to their patients. Such a strategy may have a reasonable chance of acceptance.

Finally, it is worth noting that, although it is now almost routine practice to provide dermal analgesia in children before venous cannulation, patterns of practice vary in adults.⁴ Research has demonstrated that venous cannulation, irrespective of cannula size and intradermal injection of local anaesthetics, is a painful experience for adults.^{17,18} Injection of local anaesthetics into the dermis may also compound procedure related side effects in patients who have needle 'phobia' and result in increased numbers of contaminated sharps with their associated dangers.¹⁹ Awareness of the increasing importance of patient comfort on the basis of humanitarian grounds and in terms of quality of care have led to recommendations to extend the practice of providing topical analgesia to include adults as well as children.¹⁹ The results of this study may help institutions in developing suitable strategies for managing the pain of venous cannulation in adults. It has been argued that intra-dermal local anaesthetic makes cannulation difficult because swelling from the injection may obscure the vein.²⁰ The other drawbacks are accidental venous puncture, bruising, pain and the need to find another cannulation site.²⁰ This study confirmed previous reports in children that the EMLA® patch does not produce local reactions that may interfere with cannulation.^{5,6}

In conclusion, this study showed that application of the EMLA® patch on the dorsum of the hand before venous cannulation was effective in reducing the pain of venous cannulation and the incidence of vaso-vagal side effects in adult outpatients. Local skin reactions were negligible and the application time did not limit its feasibility in an outpatient facility. Most patients were willing to pay for the EMLA® patch before future venous cannulation.

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References

- 1 Langham BT, Harrison DA. Local anaesthetics: does it really reduce the pain of insertion of all sizes of venous cannula? *Anaesthesia* 1992; 47: 890-1.
- 2 Pavlin DJ, Links S, Rapp SE, Nessly ML, Keyes HJ. Vaso-vagal reactions in an ambulatory Surgery Center. *Anesth Analg* 1993; 76: 931-5.
- 3 Langham BT, Harrison DA. The pressor response to venous cannulation: attenuation by prior infiltration with local anaesthetic. *Br J Anaesth* 1993; 70: 519-21.
- 4 Steward DJ. Management of childhood pain: new approaches to procedure-related pain. *J Paediatr* 1993; 122(Suppl): S1-46.
- 5 Chang PC, Goresky GV, O'Connor G, et al. A multicentre randomized study of single-unit dose package of EMLA patch vs. EMLA 5% cream for venepuncture in children. *Can J Anaesth* 1994; 41: 59-63.
- 6 Nilsson A, Boman I, Wallin B, Rotstein A. The EMLA patch - a new type of local anaesthetic application for dermal analgesia in children. *Anaesthesia* 1994; 49: 70-2.
- 7 Hallén B, Olsson GL, Uppfeldt A. Pain-free venepuncture. Effect of timing of application of local anaesthetic cream. *Anaesthesia* 1984; 39: 969-72.
- 8 Hallén B, Carlsson P, Uppfeldt A. Clinical study of a lignocaine-prilocaine cream to relieve the pain of venepuncture. *Br J Anaesth* 1985; 57: 326-8.
- 9 Gunawardene RD, Davenport HT. Local application of EMLA and glycerol trinitrate ointment before venepuncture. *Anaesthesia* 1990; 45: 52-4.
- 10 Maddi R, Horrow JC, Mark JB, Concepcion M, Murray E. Evaluation of a new cutaneous topical anesthesia preparation. *Reg Anesth* 1990; 15: 109-12.
- 11 Moller C. A lignocaine-prilocaine cream reduces venipuncture pain. *Ups J Med Sci* 1985; 90: 293-8.
- 12 Maunskela E-L, Korpela R. Double-blind evaluation of a lignocaine-prilocaine cream (EMLA) in children. Effect on the pain associated with venous cannulation. *Br J Anaesth* 1986; 58: 1242-5.
- 13 Robieux I, Eliopoulos C, Hwang P. Pain perception and effectiveness of the eutectic mixture of local anesthetics in children undergoing venipuncture. *Pediatr Res* 1992; 32: 520-3.
- 14 Robieux IC, Kumar R, Rhadhakrishnan S, Koren G. The feasibility of using EMLA cream in Pediatric Outpatient Clinics. *The Canadian Journal of Hospital Pharmacy* 1990; 5: 235-6.
- 15 Santacana E, Aliaga L, Bayo M, Vilanova F, Villar Landeira JM. EMLA cream for 15 or 30 min before venopuncture. *Reg Anesth* 1994; 19(Suppl): 24.
- 16 Nott MR. Relief of injection pain in adults. EMLA cream for 5 minutes before venepuncture. *Anaesthesia* 1990; 45: 772-4.
- 17 Dennis AR, Leeson-Payne CG, Langham BT, Aitkenhead AR. Local anaesthesia for cannulation. Has practice changed? *Anaesthesia* 1995; 50: 400-2.
- 18 Van den Berg AA, Abeysekera RMMS. Rationalising venous cannulation: patient factors and lignocaine efficacy (Letter). *Anaesthesia* 1993; 84: 84.
- 19 McEwen AW. Painless venous cannulation - a childish approach (Letter). *Anaesthesia* 1993; 48: 1021.
- 20 Harrison N, Langham BT, Bogod DG. Appropriate use of local anaesthetic for venous cannulation. *Anaesthesia* 1992; 47: 210-2.