Xylocaine® 10% Pump Spray as topical anaesthetic for venepuncture pain

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**Background:** Cutaneous anaesthesia for venepuncture pain can be achieved using various topically applied local anaesthetic formulations. Xylocaine® 10% Pump Spray containing lignocaine hydrochloride and 95% ethanol is exclusively recommended for mucosal anaesthesia. However, this formulation is readily able to penetrate skin. This study investigated whether topical pre-treatment with Xylocaine® 10% Pump Spray could facilitate anaesthesia for venepuncture.

**Methods:** A single-centre, prospective, randomised, double-blind placebo-controlled trial was conducted. One hundred patients were enrolled. The control and intervention groups had 0.5 ml saline and 0.5 ml Xylocaine® applied for 20 min to preselected venepuncture sites. Pain associated with an 18-gauge cannula venepuncture was rated on an 11-point Numerical Rating Scale. A two-point or 30% reduction in pain would be deemed clinically significant.

**Results:** Pain scores were lower (p = 0.001) in the Xylocaine® (median 2; 95% CI 2–3) than the saline (median 4; 95% CI 3–5) group. Moderate-to-severe pain occurred in fewer Xylocaine® (18%) than saline (42%) treated patients (relative risk 0.43, CI 0.22 to 0.48; NNT = 5).

**Conclusion:** Topical Xylocaine® 10% Pump Spray pre-treatment provided a time-effective method of reducing venepuncture-associated pain.

**Keywords:** local anaesthesia, venepuncture pain, Xylocaine® 10% Pump Spray

Introduction

A patient's only clear recollection of the anaesthetic process may be the pre-induction, painful, venous cannulation. Ameliorating venepuncture-related pain may greatly improve a patient's rating of his/her anaesthetic experience.¹

Previous research has indicated that topical Xylocaine® Pump Spray effected sufficient skin anaesthesia to increase the threshold for the perception of electrical current,² and that it significantly decreased pain perception during burns dressing changes when applied to the broken skin of the graft donor site.³ We investigated whether Xylocaine® 10% Pump Spray could efficiently provide sufficient cutaneous analgesia to reduce venepuncture-related pain. A standard dose of Xylocaine® Pump Spray was sprayed onto a 2 cm square gauze pad. This gauze pad was affixed to the skin over the intended venepuncture site using a translucent, adhesive dressing.

Kanai et al. observed an increase in skin electrical current perception threshold after only a 30-min application of either lignocaine spray or lignocaine emulsion. While this study reported faster onset of cutaneous ‘analgesia’ with lignocaine spray than with the lignocaine emulsion:² we cannot identify previous research investigating Xylocaine® Pump Spray to ameliorate venepuncture pain. Based on the research of Kanai et al.³ and a small pilot study we conducted, we decided to investigate the effectiveness of a 20-min application time.

**Methods**

A single-centre, prospective, randomised, double-blind, placebo-controlled trial was conducted. University Human Research Ethics Committee approval was obtained. Eligible patients provided prior, written, informed consent. Inclusion criteria comprised a minimum age of 18 years, elective surgery, pregnant patients greater than 38 weeks' gestation presenting for Caesarean section, and patients who did not already have an appropriate size, satisfactorily functioning intravenous cannula sited before arrival in theatre. Exclusion criteria included females of childbearing age in whom early pregnancy had not been excluded, decreased level of consciousness or neurological deficit (rendering a patient incapable of performing the pain score reliably), broken skin over the proposed venepuncture site, patients having received sedation or analgesia within the last 12 h, and/or a history of adverse reactions to lignocaine.

Patients were randomised into two groups: group X who received the treatment (Xylocaine® 10% Pump Spray, AstraZeneca, North Ryde, NSW), and group S who received the normal saline placebo. A numbered computer-generated randomisation sheet was used.⁴ The two investigators were blinded to group allocations.

One of the two investigators identified and marked an appropriate forearm vein and venepuncture site between the elbow and the hand. The venepuncture site was prepared using a 70% isopropyl alcohol-soaked wipe (Webcol™, Covidien, Dublin, Ireland). Only the anaesthesia assistant was unblinded to the patient group allocation. This assistant impregnated a 2-cm square, double-layered piece of gauze with either five pumps of Xylocaine® Spray or 0.5 ml of sterile, normal saline. The 0.5 ml of a 10% solution contains 50 mg lignocaine. This piece of gauze was applied to the venepuncture site using an occlusive, transparent dressing (OpSite Flexigrid®, Smith & Nephew, London, UK). After a 20-min application time, the dressing was removed by one of the two investigators and an 18-gauge cannula (B|Braun Vasofix® Safety, Melsungen, Germany) was sited.

The investigator then requested the patient to rate needle insertion related pain using an 11-point, 0–10, Numerical Rating Scale. The Numerical Rating Scale was chosen due to its ease of interpretation for patients and its usefulness in both literate and illiterate patients.⁵ Numerical rating scale anchors were no pain...
(0) and most severe pain imaginable (10). If the initial attempt failed, the patient was asked to complete the score for the attempted venepuncture before the second attempt was made. Second attempts were not scored.

We decided beforehand that a clinically significant reduction in pain would be indicated by a two-point decrease in the 11-point numerical rating pain scale.

A power calculation using PASS version 12 (Hintze, J. 2013. PASS 12. NCSS, LLC. Kaysville, Utah, USA; www.ncss.com), revealed that 42 individuals per group would be needed to detect a two-point difference (standard deviation 2.8) with alpha 0.05 and power 90%. We decided to study 50 patients per group.

SPSS® version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows. Version 22.0, IBM Corp, Armonk, NY, USA) was used for data analysis. The 95% confidence intervals (95% CI) and number needed to treat for non-parametric data were calculated using EpiCalc version 1.02 (Gilman, J. and Myatt, M. (1998), EpiCalc 2000 1.02). Demographics and baseline outcomes were compared between the two groups using chi-square tests for categorical variables and Student’s t-tests for continuous, normally distributed variables. Pain scores and further ordinal data were compared using non-parametric Mann Whitney U-tests. Numerical Rating Scale pain scores were categorised as mild (1–4), moderate (5–7), and severe (8–10). We also dichotomised pain outcomes into ‘nil-to-mild’ (Numerical Rating Scale 0–4) and ‘moderate-to-severe’ (Numerical Rating Scale 5–10) groups. A p-value of < 0.05 was considered statistically significant. We considered clinical significance as being a two-point or 30% reduction in pain scores. Parametric data are presented as mean, standard deviation (SD) and 95% confidence intervals. Non-parametric data are presented as median, interquartile ranges (IQR) and 95% CI.

Results
One hundred patients participated in the study. No between-group demographic differences were identified (Table 1). No adverse reactions or Xylocaine® spray related skin changes were observed.

Median pain scores were reduced from 4 to 2 (p = 0.001) in groups S and X respectively (Table 2 and Figure 1).

No between-group differences in age or gender were identified.

The median pain score was reduced from 4 in the saline group (Group S) to 2 in the Xylocaine® group (Group X).

Pain scores were lower in the intervention group (p = 0.006), being rated as absent (20% vs. 4%), mild (62% vs. 54%), moderate (18% vs. 32%), and severe (0 vs. 10%) in the X and S groups (Figure 2).

Dichotomisation revealed a higher incidence of ‘nil-to-mild’ (82% vs. 58%) than ‘moderate-to-severe’ (18% vs. 42%) venepuncture-related pain (p = 0.009) in group X than in group S (Figure 3). Xylocaine® venepuncture site pre-treatment reduced the risk of ‘moderate-to-severe’ pain by 57% (risk ratio 0.43; 95% CI 0.22–0.48). The number needed to treat (NNT) to decrease pain from the ‘moderate-to-severe’ to ‘nil-to-mild group’ was 5.

Table 1: Demographic data

| Factor          | Group S       | Group X       | p-value |
|-----------------|---------------|---------------|---------|
| Mean age in years | 44.1 ± 15.8 (CI95% 39.8–48.8) | 43.4 ± 15.6 (CI95% 39.1–47.7) | 0.819   |
| Gender (% male) | 40%           | 28%           | 0.205   |

Table 2: Pain scores

| Group | n  | Median | 95% CI | Interquartile range | Range | p-value |
|-------|----|--------|--------|--------------------|-------|---------|
| Group S | 50 | 4      | 3–5    | 3–5                | 0–10  | 0.001*  |
| Group X | 50 | 2      | 2–3    | 1–4                | 0–7   |         |

Discussion
We hypothesised that a 20 min application of Xylocaine® 10% Pump Spray would ameliorate venepuncture pain compared with a placebo. We observed a statistically and clinically significant reduction in pain scores compared with the placebo. A NNT of 5 was required to shift pain from the ‘moderate-to-severe’ to ‘nil-to-mild group’.

Figure 1: Pain score data.
Pain score ranges and medians with 95% CI.

Figure 2: Pain categories.
Graph of the percentage of patients within each pain category for the saline (S) and Xylocaine® (X) groups. Pain categorisation: 0 (nil), 1–4 (mild), 5–7 (moderate) and 8–10 (severe)
interspersed by extracellular lipid lamellae. Envelope surrounding keratin-containing corneocytes to its specific structure, consisting of a cornified proteinaceous teleological defence barrier. Its impermeability can be attributed must first cross the relatively impermeable stratum corneum, a purified water. Xylocaine® 10% Pump Spray's formulation and its contains 24.1% m/v ethanol 95%, polyethylene glycol 400 and application of an occlusive dressing over the treated skin area. 17 Enhancers (e.g. water, ethanol, polyethylene glycol) or the concentration, the addition of solvent vehicles or penetration across the stratum corneum. 16−20 Mechanisms to enhance drug A recurring theme is how to facilitate transfer of topical lignocaine properties facilitate rapid lipid membrane penetration and onset ionised fraction at physiological pH. These physico-chemical lipid-solubility and high pKa (7.8) with consequently a high un-ionised properties of tissue. 18 Ethanol is thought to cause fluidisation of stratum corneum’s lipid bilayer. Both ethanol and polyethylene glycol probably enhance drug transfer by altering the solvent properties of tissue. 19 Ethanol is thought to cause fluidisation of intercellular lipids. 18,20 Interestingly, Xylocaine® 10% Pump Spray contains 24.1% m/v ethanol 95%, polyethylene glycol 400 and purified water. Xylocaine® 10% Pump Spray’s formulation and its application using an occlusive dressing fulfils many of the aforementioned criteria to enhance cutaneous drug transfer.

Despite previous research indicating effective blunting of dermal perception of electrical current and the skin-penetrating attributes of Xylocaine® 10% Pump Spray, it has still been used almost exclusively for mucous membrane analgesia. 3 To our knowledge, no previous study has investigated its ability to reduce venepuncture pain.

Two commercially available topical preparations are used for ameliorating venepuncture pain. EMLA® (eutectic mixture of 2.5% lignocaine and 2.5% prilocaine) is an oil-in-water emulsion containing a high concentration of 20% lignocaine within each emulsion droplet. The low overall concentration (5% lignocaine) of local anaesthetic, however, carries a low risk of toxicity. 21 EMLA® provides excellent analgesia when applied for 1 h prior to venepuncture. 22 Amethocaine topical gel (Ametop 4%, Smith & Nephew, Hull, England) requires a 30–45 min application time to be effective. A Cochrane systematic review reported amethocaine topical gel to be more effective than EMLA® at reducing venepuncture pain. It is not currently available in South Africa. 23

In this initial study, we elected to simply compare Xylocaine® Pump Spray with a placebo, and will in the future need to compare it directly with EMLA®. EMLA® needs to be applied 1 h prior to the needling procedure to be effective. 22 Our study indicated that Xylocaine® 10% Pump Spray was effective after only 20 min. We did not compare directly with EMLA® or amethocaine gel but the short application time needed may enable a greater percentage of patients to receive topical local anaesthesia prior to venous cannulation. It would be interesting to investigate the speed of onset of alkalised topical lignocaine.

Mucous membrane application yields the highest serum concentrations after topical lignocaine application. 24 Despite the use of high lignocaine concentrations (8–10%), dermal application appears safe. Even after Xylocaine® 10% topical spray (70.3 ± 23.3 mg) was applied to broken skin, serum levels were still 25 times lower than the toxic concentration of 5 µg/ml. 2 We would expect very low serum lignocaine concentrations following the cutaneous application of a gauze pad impregnated with only 50 mg of lignocaine. Nonetheless, we would need to measure serum lignocaine concentrations before we could perform a similar study in children.

Ametop is not available in South Africa. Single applications of 1 g of EMLA® and Xylocaine® spray at the dose used in this study would amount to a cost of R6.90 and R1.05, respectively. This equates to an 86% cost reduction by using Xylocaine® instead of EMLA®. The cost of the plastic dressing remains the same in both instances.

Our study indicates that 10% Xylocaine® spray would potentially provide a rapidly effective, readily available, cheaper alternative to blunt venepuncture pain.

Disclosure statement
No potential conflict of interest was reported by the authors.

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References

1. Chyun D. Patients’ perceptions of stressors in intensive care and coronary units. Focus Crit Care. 1989;16:206–11.

2. Kanai A, Suzuki A, Okamoto H, et al. Comparison of cutaneous anesthetic effect of 8% Lidozone spray with lidocaine patch. Pain Med. 2010;11(3):472–75. https://doi.org/10.1111/j.1526-4637.2009.00790.x

3. Desai C, Wood FM, Schug SA, et al. Effectiveness of a topical local anesthetic spray as analgesia for dressing changes: a double-blinded randomised pilot trial comparing an emulsion with an aqueous lidocaine formulation. Burns. 40(1):106–12. doi:10.1016/j.burns.2013.05.013.

4. Dallal G. [cited February 2, 2018]. Available from: http://randomization.com

5. Hjernestad M, Fayers P, Haugen D. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manag. 2011;41(6):1073–93. https://doi.org/10.1016/j.jpainsymman.2010.08.016

6. Lehmann E. Non-Parametrics: statistical methods based on ranks, revised. 1st ed. New York, NY: Springer; 1998.

7. Hawker G. Measures of adult pain. Meas Pathol symptoms. 2011:63(511):240–52.

8. Vijayan R, Scott G, Brownlie W. Out of sight, but not out of mind? Greater reported pain in patients who spontaneously look away during venipuncture. Eur J Pain. 2015;19(1):97–102. https://doi.org/10.1002/ejp.2015.19.issue-1

9. Croxtall J. Lidozone/tetracaine medicated plaster: in minor dermatological and needle puncture procedures. Drugs. 70(16):2113–20.

10. Smythies J. Taking the sting out of needles. J R Soc Med. 2005;98(4):139–40.

11. Sado DM, Deakin CD. Local anaesthesia for venous cannulation and arterial blood gas sampling: are doctors using it? J R Soc Med. 2005;98:158–60. https://doi.org/10.1177/014107680509800405

12. Adriani J, Dalili H. Penetration of local anesthetics through epithelial barriers. Anesth Analg. 1971;50(5):834–41. https://doi.org/10.1213/00000539-197150050-00027

13. Berde CB, Strichartz GR. Local anesthetics. In Miller RD, Eriksson LI, Fleisher LA, et al., editors. Miller Anesthesia. 8th. ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2014:1028–1054.

14. Oshizaka T, Kikuchi K, Kadhum WR, et al. Estimation of skin concentrations of topically applied lidocaine at each depth profile. Int J Pharm. 2014;475(1–2):292–7. doi:10.1016/j.ijpharm.2014.08.046.

15. Madison KC. Barrier function of the skin: ‘La Raison d’Etre’ of the epidermis. J Invest Dermatol. 2003;121(2):231–41. https://doi.org/10.1046/j.1523-1747.2003.12359.x

16. Poonai N, Alawi K, Lim R. A comparison of amethocaine and liposomal lignocaine cream as a pain releiver before venipuncture in children. Pediatr Emerg Care. 2012;28(2):104–8.

17. Prausnitz M, Elias P, Franz T. Skin barrier and transdermal drug delivery. In: Bolognia J, Jorizzo J, Schaffer J, editors. Dermatology. 3rd ed.. Philadelphia, PA: Elsevier Health Sciences; 2012. p. 2065–73.

18. Williams A, Barry B. Penetration enhancers. Adv Drug Deliv Rev. 64(Supplement):128–37.

19. Chantasart D, Li S. Structure enhancement relationships of chemical penetration enhancers in drug transport across the stratum corneum. Pharmaceutics. 2012;4:71–92. doi:10.3390/pharmaceutics4010071.

20. Horita D, Hatta I, Yoshimoto M. Molecular mechanisms of action of different concentrations of ethanol in water on ordered structures of intracellular lipids and soft keratin in the stratum corneum. Biochem Biophys Acta. 2015;1848(5):1196–202. https://doi.org/10.1016/j.bbamem.2015.02.008

21. Moller C. A Lignocaine-prilocaine Cream Reduces Venipuncture Pain. Upsala J Med Sci. 1985;90:293–8. https://doi.org/10.3109/03009738509178485

22. EMLA 5% (Cream) [Package Insert]. Bryanston (RSA): AstraZeneca Pharmaceuticals (Pty) Ltd; 2012.

23. Lander J, Weltman B, So S. EMLA and amethocaine for reduction of children’s pain associated with needle insertion. Cochrane Database Syst Rev. 2006;19(3):CD004236.

24. Becker D, Reed K. Local anesthetics: review of pharmacological considerations. Anesth Prog. 2012;59(2):90–102. https://doi.org/10.2344/0003-3006-59.2.90

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