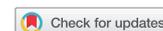# Xylocaine® 10% Pump Spray as topical anaesthetic for venepuncture pain

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Background: Cutaneous analgesia 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 analgesia 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.*[2] 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.[6]

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).[7] 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.
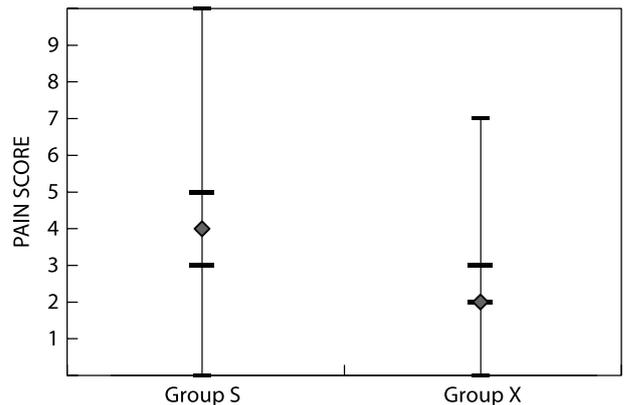

Figure 1: Pain score data.
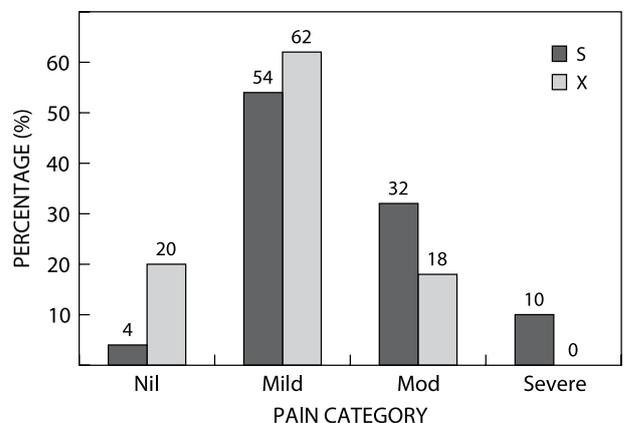Pain score ranges and medians with 95% CI.

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)

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'.

Table 1: Demographic data

Factor	Group S	Group X	*p*-value
Mean age in years (95% CI)	44.1 ± 15.8 (CI$_{95\%}$ 39.8–48.8)	43.4 ± 15.6 (CI$_{95\%}$ 39.1–47.7)	0.819
Gender (% male)	40%	28%	0.205

Table 2: Pain scores

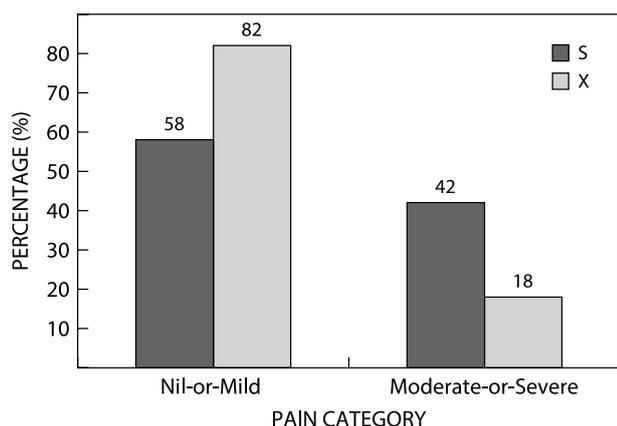| Group	*n*	Median	95% CI	Interquartile range	Range	*p*-value
Group S	50	4	3–5	3–5	0–10	0.001*
Group X	50	2	2–3	1–4	0–7	

Figure 3: Dichotomisation of pain scores.

Percentage of patients in saline (S) and Xylocaine® (X) groups after dichotomisation of the pain scores into 'nil-to-mild' (Numerical Rating Scale 0–4) and 'moderate-to-severe' pain (Numerical Rating Scale 5–10); p = 0.009.

Techniques previously investigated to ameliorate venepuncture pain have included gaze aversion, hypnosis, music distraction, performing a Valsalva manoeuvre, administering oral sucrose solutions to children, local application of cold using ethyl chloride, local capsaicin application, subcutaneous local anaesthetic infiltration, and topical local anaesthetic.[8,9]

Subcutaneous local anaesthetic infiltration typically elicits a VAS score of 1–2, significantly less painful than intravenous cannulation.[10] Nonetheless, many physicians still eschew its use, rationalising that it replaces one painful needling procedure with another, causes subcutaneous skin distortion and more difficult cannula siting. In addition, lack of drug and equipment, particularly in wards, impedes its use.[11]

Lignocaine has a low molecular weight (234.34 Dalton), high lipid-solubility and high pKa (7.8) with consequently a high un-ionised fraction at physiological pH. These physico-chemical properties facilitate rapid lipid membrane penetration and onset of cutaneous anaesthesia once the sub-epidermal nerve endings have been reached.[12–14] However, cutaneously applied lignocaine must first cross the relatively impermeable stratum corneum, a teleological defence barrier. Its impermeability can be attributed to its specific structure, consisting of a cornified proteinaceous envelope surrounding keratin-containing corneocytes interspersed by extracellular lipid lamellae.[15]

A recurring theme is how to facilitate transfer of topical lignocaine across the stratum corneum.[16–20] Mechanisms to enhance drug transfer across the stratum corneum include using a high drug concentration, the addition of solvent vehicles or penetration enhancers (e.g. water, ethanol, polyethylene glycol) or the application of an occlusive dressing over the treated skin area.[17] Both the addition of water and the use of an occlusive dressing serve to hydrate the skin. It is unclear exactly how cutaneous hydration enhances drug penetration. Postulated mechanisms include equilibration of the water content of the stratum corneum and dermis, or that water saturation disrupts the stratum corneum's lipid bilayer. Both ethanol and polyethylene glycol probably enhance drug transfer by altering the solvent properties of tissue.[18] Ethanol is thought to cause fluidisation of intercellular lipids.[19,20] 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.[2] 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 alkalinised 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.[3] 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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