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ORIGINAL ARTICLE

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A randomized controlled trial comparing Ametop™ with placebo for reducing pain associated with local anesthetic skin infiltration before neuraxial anesthesia in parturients

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ABSTRACT
Background: Between 10–22% of the general population experience needle phobia. Needle phobic parturients are at increased risk of adverse outcomes. We assessed the efficacy of topical Ametop™ (tetracaine 4%) gel in reducing the pain associated with local anesthetic skin infiltration before neuraxial block in non-laboring women.
Methods: This was a prospective, randomized, double-blind, placebo-controlled study. Ametop™ or placebo was applied to the skin of the lower back at least 20 min before neuraxial block using a standardized technique with 1% lidocaine skin infiltration. The primary outcome was numeric pain score (0–10) 30 s after lidocaine infiltration. Groups were compared using Welch's t-test.
Results: Thirty-six subjects in each group were analyzed. There was a statistically significant difference in the mean (standard deviation) pain score between the Ametop™ and the placebo groups: 2.36 ± 1.80 and 3.51 ± 2.22, respectively (P=0.019). There were no significant adverse events.
Conclusion: The mean numeric pain score in the Ametop™ group was 33% lower compared to the placebo group. Topical Ametop™ gel applied at least 20 min before local anesthetic infiltration of the skin prior to neuraxial block in elective cesarean delivery may be a useful adjunct in needle phobic women.

Keywords: Ametop™; Neuraxial block; Lidocaine

Introduction

Needle phobia is recognized as a specific disorder in both the ICD-10 and the DSM-IV classifications of mental disorders.[1,2] The incidence of needle phobia in the general population is estimated at 10–22%.[3–5] The incidence in hospitalized patients is likely to be lower because such patients tend to avoid medical care.[4] The condition is characterized by an irrational fear of any medical procedure that involves the use of needles and can have a significant impact on the antenatal care of affected women. A retrospective cohort study of 112 needle phobic women found that they registered later with antenatal services, consented less often to blood tests at the consultation booking and, if cesarean delivery (CD) was required, had a significantly higher demand for general anesthesia,[6] which results in exposure to greater perioperative risk of gastric aspiration, failed intubation and increased postoperative pain.[6] In the 2011 triennial report of the Confidential Enquiries into Maternal Deaths in the UK, one death was reported following thromboembolism after CD in a needle phobic parturient who refused low molecular weight heparin (LMWH) thromboprophylaxis.[7] Without anticoagulant prophylaxis the incidence of venous thromboembolism following CD has been reported as 0.5% and LMWH can reduce this risk by 70% in surgical patients.[8,9]

It has been our experience that a subgroup of patients fears the anesthetic procedure, specifically needle insertion for neuraxial block, more than the planned surgery. While the underlying psychological mechanism involved in irrational fear of needles is multifaceted, part of the fear lies in the anticipated pain associated with needle puncture. In the case of local anesthetic (LA) infiltration, the accompanying burning sensation can be experienced as moderate to severe.[10]

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Ametop™ (Smith & Nephew, Saint-Laurent, QC, Canada) is a highly lipid soluble ester type LA gel composed of 4% tetracaine (also known as amethocaine). It has been licensed in Canada since 1998. Ametop™ penetrates the outer layer of the epidermis faster than EMLA®,[11] has faster onset (30–45 min compared to 1–2 h) and produces more potent anesthesia.[12] A Cochrane review in 2010 comparing the two agents for venepuncture or subcutaneous injection in children concluded that Ametop™ provided better analgesia.[12] The efficacy of Ametop™ gel in reducing the pain associated with LA skin infiltration before neuraxial block in pregnant patients has not been studied. This study was designed to assess discomfort during LA skin infiltration before neuraxial block in non-laboring parturients.

Methods

Approval was obtained from the local ethics committee (University of British Columbia, Vancouver, Canada, certificate number H13-00771). The trial was registered with ClinicalTrials.gov (NCT01864213). This was a prospective, randomized, double-blind, placebo-controlled study developed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.[13] The primary anesthesiologist, research assistant, and the patient were blinded to group allocation. We hypothesized that Ametop™ application at least 20 min before skin infiltration with LA would reduce the numeric pain scale (NPS) rating in non-laboring parturients by at least 33% compared to placebo.

Term parturients undergoing an elective procedure under neuraxial block were recruited between June 3, 2013 and October 8, 2013. Exclusion criteria were: patients in labor, body mass index (BMI) >45 kg/m^2, history of back surgery, allergy to ester-type LA or para-amino benzoic acid, Ametop™ *in situ* for less than 20 min, infiltration of the skin outside the area previously covered by the cream or subjects unable to communicate sufficiently either in English or via a translator.

Following written informed consent, women were randomized using a computer-generated table into either the Ametop™ or the placebo groups. The placebo was a cream of similar color and texture (Mediderm™ base cream, Medisca, Montreal, QC, Canada). An anesthesiologist not involved in direct patient care opened a sealed envelope containing the group allocation and prepared the assigned cream in a sterile 3 mL syringe. It was applied by the treating anesthesiologist. This maintained appropriate blinding of the treating anesthesiologist while still permitting application of the cream over their chosen site. In the preoperative holding area, landmarks on the patient's back were identified and the study cream (total 3 g, equating to approximately 2.5 mL in the syringe) was applied to the skin across two lumbar intervertebral spaces, an area of approximately 10 cm $\times$ 8 cm, and was then covered with an occlusive dressing (Tegaderm™ Film 12 cm $\times$ 10 cm, 3M Health Care, London, ON, Canada). A skin marker was applied at two opposite corners of the dressing to show where the cream had been applied when the dressing and cream were removed in preparation for neuraxial block. The time of cream application was noted.

On the operating table the patient was positioned in the sitting position. Standard monitors (non-invasive blood pressure cuff, pulse oximeter and electrocardiogram leads) were applied. The occlusive dressing was removed, the cream was wiped off using paper towels and the time noted. The skin was prepared with 2% chlorhexidine gluconate (ChloraPrep® stick, BD, Mississauga, ON, Canada) antiseptic. Skin infiltration with LA and neuraxial needle insertion were performed by a staff anesthesiologist or a clinical research fellow blinded to group allocation. To avoid influencing the patient's perception of the needle insertion or LA injection, the anesthesiologist informed the patient using the standardized phrase "I am about to inject the LA now". Under aseptic conditions a standardized technique of LA infiltration was performed. A 3.8 cm 25-gauge needle was inserted perpendicular to the skin in the area from which the cream had been removed; 1% lidocaine 1 mL was slowly infiltrated to raise a subdermal wheal and then the needle was advanced approximately 2 cm into the tissues. The needle was slowly withdrawn while injecting 1% lidocaine 3 mL over 10–15 s. No needle redirection occurred. Thirty seconds after LA infiltration, but before insertion of the neuraxial or introducer needle, the patient was asked to rate the pain of the infiltration on a NPS with zero corresponding to no pain and 10 being the worst pain imaginable. This was recorded by the research assistant who was also blinded to the subject's group allocation. The anesthesiologist then performed neuraxial injection in the usual manner.

Statistical analysis

Sample size calculation was based on a previously published result for the mean NPS of LA infiltration in non-laboring parturients of 40 out of 100 with a standard deviation (SD) of 20.[14] Using a power of 0.80 and a one-sided alpha of 0.05, it was determined that a sample size of 30 patients per group would be required in order to detect a 33% reduction in NPS. We hypothesized that a reduction of 33% in NPS would be a clinically significant result. Allowing for withdrawals and exclusions it was planned to recruit a minimum of 35 patients per group. Primary outcome was the NPS at 30 s after LA infiltration. Data are presented as mean $\pm$ SD with 95% confidence intervals (CI). Groups were compared using the Welch's t-test, an adaptation of the Student's