Novel topical formulation of lidocaine provides significant pain relief for intrauterine device insertion: pharmacokinetic evaluation and randomized placebo-controlled trial

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Objective: To investigate the pharmacokinetics, safety, and analgesic efficacy of a novel topical formulation of lidocaine at insertion of an intrauterine device (IUD).
Design: Randomized controlled trial; phase-I and phase-II studies.
Setting: University and public hospitals.
Patient(s): Women aged ≥ 18 years who wanted to receive an IUD. Four women were parous in phase I; all in phase II were nulliparous.
Intervention(s): A single, 8.5-mL dose of lidocaine formulation (SHACT) was administered (to the portio, cervix, and uterus) with a specially designed applicator.
Main Outcome Measure(s): The phase-I study (single-arm) was designed for pharmacokinetic assessment; the phase-II study (randomized) was intended for investigation of efficacy and safety.
Result(s): From the phase-I study (15 participants), mean pharmacokinetic values were: maximum plasma concentration: 351 ± 205 ng/mL; time taken to reach maximum concentration: 68 ± 41 minutes; and area under the concentration–time curve from 0 to 180 minutes: 717 ± 421 ng*h/mL. Pain relief was observed with lidocaine vs. placebo in the phase-II study (218 women, randomized). Mean visual analog scale score for maximum pain during the first 10 minutes after IUD insertion was 36% lower with lidocaine than with placebo (28.3 ± 24.6 vs. 44.2 ± 26.0). Pain intensity was also significantly lower in the lidocaine group at 30 minutes. On average, 3 of 4 patients will have less pain with lidocaine than with placebo. Adverse events were similar in the placebo and lidocaine groups. No serious adverse events were reported.
Conclusion(s): Lidocaine provides pain relief lasting for 30–60 minutes for women undergoing IUD insertion, without any safety concerns. Further studies of this lidocaine formulation, for IUD insertion and other clinical applications, are planned.
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Key Words: Intrauterine device, lidocaine, pain, pharmacokinetics, topical anesthetic

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Intrauterine devices (IUDs) provide reliable, long-term contraception from a single insertion procedure (1, 2). However, the insertion of an IUD can be associated with significant levels of pain, which for many women is a major obstacle to IUD use (3). This

method of contraception is considered to be underutilized, with only 7.6% of women of reproductive age in developed countries adopting the IUD, and 14.5% in developing countries (4).

The role of the capsaicin and heat receptor transient receptor potential vanilloid (TRPV1) has been explored in the human cervix and the uterus. This work identified peripheral sensory innervations in both the cervix and uterus in nonpregnant women (5), strengthening the rationale for using topical anesthetic for IUD insertion. Few studies have provided robust evidence that topical anesthetics provide pain relief for women undergoing IUD insertion (6). Two Cochrane reviews showed a lack of clinically relevant pain relief with the available pharmacologic therapies, although topical lidocaine was identified as warranting further investigation (7, 8). More recent reviews of intrauterine anesthesia, published in 2012 and 2013, also found insufficient evidence for its use in IUD insertion (3, 9). One randomized study was identified, with a significantly lower pain score among women treated with 2% lidocaine (Instillagel) vs. either placebo or no treatment (10). However, the results need further substantiation, because the investigators were not blinded, and the authors considered the study to be only preliminary. In 2012, a randomized trial of 1% lidocaine paracervical block for IUD insertion showed only a trend toward a reduced visual analog scale (VAS) pain score with the lidocaine, compared with no anesthetic (11).

A novel topical formulation of lidocaine (short-acting 4% viscous solution; SHACT) has been developed (Pharmanest AB) for gynecologic application. The viscosity of this formulation increases with increasing temperature, so that leakage after gynecologic administration is minimized, and delivery of lidocaine to the intended tissues is prolonged. We performed phase I and phase II studies to investigate the pharmacokinetics, efficacy, and safety of this formulation of lidocaine as an anesthetic for IUD insertion.

MATERIALS AND METHODS

Phase I: Single-Arm Pharmacokinetic Study

This single-center study was performed at the Karolinska University Hospital, Stockholm, Sweden in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was reviewed and approved by the Stockholm Regional Ethical Review. Women aged $\geq$18 years who wanted to receive an IUD were eligible to participate, with no restrictions based on previous childbirth. Exclusion criteria included cervical infection, current pregnancy, pelvic inflammation disease within the last month, intolerance to acetaminophen, cervical or uterine cancer, and intake of analgesics within the 24 hours preceding IUD insertion. No restriction was put on the type of IUD. All participants provided signed informed consent after receiving verbal and written information about the study.

The lidocaine was administered 5 minutes before IUD insertion, as a single, 8.5-mL dose. A speculum, and an applicator with a diameter of 3.7 mm, were used for application: 1 mL was put onto the surface of the portio; 2 mL were put into the cervical canal; and 5.5 mL were put into the uterine cavity. After administration, but before IUD insertion, the degree of discomfort was ascertained by asking: "Did you experience any discomfort associated with administration of the study drug?" Participants were asked to choose their answer from the following options: "no," "a little," "some," "high level," and "very high level." The insertion of IUDs was performed according to the recommendations of their manufacturers.

Blood samples (4 mL) were taken at baseline, and at 5, 10, 20, 30, 45, 60, 120, and 180 minutes after administration. In each sample, the plasma level of lidocaine was determined, to calculate the following pharmacokinetic parameters: maximum plasma concentration (C_{max}), time taken to reach maximum concentration (t_{max}), and area under the concentration–time curve from 0 to 180 minutes (AUC_{0-180}). Lidocaine concentration was determined using a validated liquid chromatography-mass spectrometry/mass spectometry (LC-MS/MS) method, with a quantitation limit of 1.0 ng/ml, accuracy of 90% of nominal value, and repeatability coefficient of variation of 12%, both at 1 ng/ml. Plasma pharmacokinetics calculations for lidocaine were performed by standard noncompartmental analysis using WinNonlin software (version 3.1, Certara).

Pain was assessed on a 100-mm VAS at 10 minutes (maximum pain experienced within 10 minutes of IUD insertion), 1 hour, 2 hours, 1 day, 2 days, and 3 days after IUD insertion. An additional oral analgesic (acetaminophen) was provided, and participants recorded their use of this medication over the 4-day period after IUD insertion. Adverse events were recorded by active questioning at 3 time points: just before IUD insertion, and at 15 minutes and 2 hours after lidocaine administration. Diary entries enabled further adverse-event reporting on days 2–4.

Phase-I Statistics

A sample size of 15 was chosen, as this number should enable pharmacokinetic parameters to be determined with reasonable accuracy. Individuals with incomplete blood sampling were replaced, to ensure that the 15 study participants had complete blood sampling. The primary variables were C_{max}, t_{max}, and AUC_{0-180}. All study results are presented as mean $\pm$ SD or absolute values; no statistical comparisons were performed.

Phase II: Randomized, Double-Blind, Placebo-Controlled Study of Pain Relief

The phase II study was performed at 3 Swedish hospitals: Karolinska University Hospital, University Hospital of Linkoping, and Vrinnevi Hospital in Norrkoping. The study was reviewed and approved by the Stockholm Regional Ethical Review Board (2012/801-32). The methods and ethical standards for phase 2 were fundamentally similar to those for phase I. However, women who had previously given birth were excluded from phase II, although they were permitted in phase I.

Study participants were randomized 1:1 to receive the lidocaine or a placebo gel with similar appearance and viscosity. A randomization list was generated by the study statistician, using nQuery Advisor (Statistical Solutions Ltd.). Code

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