Topical Vapocoolant Quickly and Effectively Reduces Vaccine-associated Pain: Results of a Randomized, Single-blinded, Placebo-controlled Study

Steven Mawhorter, Lynda Daugherty, Allison Ford, Robin Hughes, Dee Metzger, and Kirk Easley

Background: Comprehensive international travel preparation often requires several vaccines. Up to 90% of adults have some fear of injections, mostly due to injection-related pain. Pediatric studies with routine vaccines have shown topical anesthetic EMLA cream (lidocaine and prilocaine, Astra Pharmaceuticals, Inc.) and the topical vapocoolant Fluori-Methane (dichlorodifluoromethane and trichlorodifluoromethane, Gebauer Co.) to be equally effective in reducing pain from vaccinations. EMLA cream is expensive and requires a 60-min application, while Fluori-Methane (FM) is immediate in onset of action and inexpensive. Skin anesthesia begins at 10°C. Fluori-Methane can briefly cool the skin to 0°C.

Methods: We studied the effectiveness of topical vapocoolant on adult clients at our international travel clinic in a randomized, controlled trial of topical FM vs. cold (4°C) saline placebo. Using a preset randomization table, participants served as their own controls, receiving placebo/control or active agent (participant blinded) in one arm (left or right), and a similar number of vaccines in the untreated arm. Vaccines were administered according to a set protocol per arm to minimize the risk of bias. Pain was measured using a modified McGill present pain intensity (PPI) pain index. Subjects rated their pain immediately and at 5 min on a six-level scale, noting treated and untreated arms separately. A questionnaire was completed on intervention preferences. Sample size was predetermined to achieve 90% statistical power estimating 25% efficacy (minimum n = 172).

Results: One hundred and eighty-five participants were enrolled; 93 FM and 92 cold saline placebo. FM-treated arms had a significant reduction in immediate pain compared to untreated arms (pain scale mean 2.2 vs. 3.1; p < .0001), and compared to placebo (mean 2.2 vs. 2.8; p < .01). Delayed pain at 5 min was not affected by FM or control (mean 1.9 vs. 2.0) compared to no intervention (pain scale 1.9). The intervention preference questionnaire indicated that participants did not find FM therapy uncomfortable. They would choose FM therapy in the future, over a cream, especially if a wait was involved.

Conclusion: The topical vapocoolant Fluori-Methane is an effective, quick, preferred, inexpensive agent for reducing vaccine-associated injection pain for international travel clients.

Steven Mawhorter, MD, DTM&H, Lynda Daugherty, RN, Allison Ford, Robin Hughes, RN, and Dee Metzger, RN: Department of Infectious Disease, Cleveland Clinic Foundation, Cleveland, OH; Kirk Easley, MS, MAp Stat: Department of Biostatistics, Emory University, Atlanta, GA.

This work was presented in part at the American Society of Tropical Medicine and Hygiene 50th Annual Meeting, Abstract 1497. Atlanta, GA, November 2001.

Reprint requests: Steven D. Mawhorter, MD, DTM&H, Cleveland Clinic Foundation, Department of Infectious Diseases/S32, 9500 Euclid Avenue, Cleveland, OH 44195.

procedures. Up to 90% of young children show serious distress during vaccination. This general level of anxiety can be severe in approximately 3.5% of Americans, and is termed injection phobia. While minimized by some, this phobia can result in syncopal attacks with significant clinical impact. Moreover, anxiety at any level can enhance pain perception, and analgesia interventions are designed to reduce both pain and anxiety.

The topical anesthetic cream EMLA (eutectic mixture of lidocaine and prilocaine, Astra Pharmaceuticals, Westborough, MA) is approved for use to reduce the pain of procedures including injections. Limitations to the use of EMLA cream are 60-min delayed onset of anesthesia, and expense (approximately US $5.00 to $7.50 per dose). As early as 1955, a volatile refrigerant liquid (ethyl chloride—a vapocoolant spray) was shown to produce cutaneous anesthesia. The agent works by reducing skin temperature to nearly 0°C for several seconds. The temporary anesthesia is achieved at a fraction of the cost of EMLA cream (approximately US $0.50 per dose). The onset of action is nearly immediate. Flammability limits safe storage in some settings.

A nonflammable related agent, Fluori-Methane (FM) (dichlorodifluoromethane and trichlorodifluoromethane, Gebauer Company, Cleveland, OH), was compared with EMLA cream in a pediatric trial and found to be equivalent with regard to pain reduction. Two placebo-controlled trials confirmed the significant pain reduction provided by topical vapocoolants in routine childhood immunizations.

We evaluated the efficacy of FM in a randomized, placebo-controlled, single-blinded protocol, assessing pain reduction in adults receiving immunizations at an international travel clinic. Our secondary objective was to gauge participant preference for or against future use of topical vapocoolants.

Methods

Participants attending the International Travelers’ Health Clinic at the Cleveland Clinic Foundation were approached regarding their willingness to participate in this Institutional Review Board (IRB)-approved study. The informed consent document was explained, and willing participants were enrolled in the study. Patients were not enrolled if they had any known sensitivity to the topical vapocoolant, or were pregnant or breast-feeding. Only patients receiving two or more vaccinations were enrolled, in order to allow patients to serve as their own controls in assessing pain reduction. The randomization procedure was developed by the study statistician (KE) and administered by the data manager. A random permuted block algorithm was used to ensure balance between the number of patients assigned to each treatment and to each arm (right or left) and to make it difficult for study personnel to know where blocks started and stopped. The study design and data analysis followed the intent-to-treat principle.

The sample size was determined using power calculations. The published efficacy of vapocoolant pain reduction is approximately 50%; we used the conservative estimate of 25% efficacy to perform power calculations. Sample size calculations were estimated based on preliminary control data on pain scores (mean = 3.0, and standard deviation = 1.5). Assuming a change on average of 25% in pain scores from the vapocoolant group relative to the control group, a sample size of 90 per group (180 total) ensured 92% statistical power to detect a treatment difference of 0.75 points at a two-sided 5% significance level if the true difference between treatments was 0.75 points. One hundred and eighty-five subjects greater than 18 years of age were randomly assigned to receive either the active agent (Fluori-Methane) or a placebo control (4°C saline-wetted cotton ball). The randomization table indicated which arm (left or right) would receive the intervention (topical vapocoolant FM or placebo/control). The other arm received no additional treatment beyond routine sterility measures.

The study was single-blinded. The participants were blinded as to which agent they received. Participants were the only ones involved in rating their pain. Since cooling is the mechanism of action known and described in the consent form, the placebo-controlled agent needed to be cold in order to provide equivalent comparison. Since topical vapocoolants may be perceived as colder than 4°C saline, individual participants received only one agent.

To avoid bias created by the possibility of variable pain according to which vaccine was administered, specific vaccinations were given in the same arm for all participants whenever possible. Since pain is subjective, we constructed the study to allow participants to serve as their own controls, treating one arm prior to vaccination, and leaving the other untreated apart from routine antisepsis measures. Pain was rated for each arm separately, immediately and at 5 min.

In order to standardize the data, we used a modified McGill present pain intensity (PPI) pain index preprinted scale for participants to rate their pain. Separate sheets were used to rate pain immediately and at 5 min. The patients were asked to rate their pain using either numerical analog estimates (0 to 10) or text (no pain to severe pain) scales. Aligning the numerical and text options resulted in a six-level scale. To accomplish the secondary objective, a six-question questionnaire was constructed. Each question allowed response
along a five-level scale from 1 (strongly disagree) to 5 (strongly agree).

**Vaccination**

Vaccines were given according to standard package insert recommendations. Depending on the patients’ specific vaccines, care was taken to balance intramuscular and subcutaneous injections between arms whenever possible. Standard skin preparation involved the use of 70% v/v alcohol and was followed for all injections.

**Vapocoolant**

A sterile cotton ball was saturated with topical vapocoolant (FM) immediately before injection behind a cardboard screen to prevent the patient from seeing which agent was used.

**Placebo**

A participant randomized to the placebo/control group received a sterile cotton ball prewetted with sterile 4°C saline behind the same cardboard screen. The saturated cold cotton ball was applied to the injection site for 15 s, using firm pressure. The area was allowed to evaporate (1 to 2 s), the skin was cleansed with alcohol, and the injection was performed according to the package insert.

**Statistical Analysis**

Repeated measures analysis of pain scores was performed with a means model using SAS Proc Mixed software (version 8) providing separate estimates of the mean by treatment and time. Specifically, a linear model using restricted maximum likelihood estimation and a heterogeneous compound symmetry variance–covariance form among the repeated measures was assumed for pain scores, and robust standard errors or parameters were used to perform statistical tests and construct 95% confidence intervals. Adjusted means and 95% confidence intervals, calculated by treatment group and time on study (immediate and 5 min), were used to summarize study results. The model-based means are unbiased with unbalanced and missing data, so long as the missing data are noninformative (missing at random). There were only 13 missing data points for the entire data set of 2,576 possible data entries, four in pain reporting and nine in the survey data. Similar analyses were performed separately for each arm. Statistical tests were two-sided. A p-value ≤ 0.05 was considered statistically significant.

**Results**

**Background Characteristics**

One hundred and eighty-five subjects were enrolled. The ratio of male to female participants was 1.1 : 1. The median number of injections received per participant was three (mean 3.34; range 2 to 6).

**Efficacy**

Topical vapocoolant quickly and effectively reduced immediate vaccine pain (Fig. 1). The greatest, and hypothesis-expected, impact was on immediate pain. The graphic results show the mean of the pain index score and 95% confidence intervals for the participants comparing the standard preparation arm (No Rx) with the intervention arm (Rx). The topical vapocoolant significantly reduced immediate vaccine-associated pain compared to the untreated arm (p < .001). Pain index scores in the untreated left and right arms were very similar for both sides of the randomization, consistent with appropriately randomized groups (data not shown). The untreated (No Rx) pain index score mean in the FM randomized group = 3.1 (95% CI 2.8–3.3%), whereas that of the untreated arm of the control randomized group (No Rx) = 3.0 (95% CI 2.8–3.3%, p > 0.50). The FM-treated immediate mean pain index score = 2.2 (95% CI 2.1–2.5%), and the control agent immediate mean pain index score = 2.8 (95% CI 2.6–3.0%). The comparison of these two groups at the immediate time point showed a statistically significant mean pain index score difference of 0.6 (95% CI 0.39–0.95%, p < .01). A trend toward

![Figure 1](https://academic.oup.com/jtm/article-abstract/11/5/267/1802071/Topical-Vapocoolant-Quickly-and-Effectively)
decreased immediate pain among the saline control participants compared to the untreated arm was noted (mean 3.0 vs. 2.8, p = .05). The pain comparison between immediate and 5-min time points is graphically depicted in Figure 2. The pain reduction continued from the immediate to 5-min time points as expected. The mean pain level at 5 min was slightly less for topical vapocoolant group than for the placebo group (p = .32). The FM 5-min mean pain index score = 1.7 (95% CI 1.5–1.9%), and the control group 5-min mean pain index score = 1.8 (95% CI 1.6–2.0%). The mean difference between the two groups at 5 min was 0.1 (95% CI 0.13–0.39, p = .32). The untreated arm mean pain index for the FM group compared to that for the control group was 2.0 vs. 1.9. At 5 min, there was a nonsignificant trend towards less pain in the arm that had received topical cold therapy than in the arm that had undergone standard pre-vaccination preparation (untreated arm) alone (p > .05).

Survey Results of Preference For or Against Future Topical Vapocoolant Use

Survey results are plotted in Figure 3. Data represent the mean of the responses, with 3 being the middle, or no difference between choices, inflection point. There was no significant difference between the topical vapocoolant and placebo group responses for any of the questions. The standard error of the results was less than 0.5 for all groups across all questions. Neither group found the cold cotton ball therapy to be uncomfortable (question 1) or messy (question 3). Neither group preferred the injection alone without the cold cotton ball therapy. When asked if they would choose cold cotton ball therapy in the future (question 4), the majority of respondents indicated agreement. When given the hypothetical option of using cream to replace the cold cotton ball therapy, participants did not prefer this method of anesthetic application (question 5). Also, as seen in question 6, the 1-h wait for onset of efficacy of cream anesthetic would be highly inconvenient for our international travel clinic clients. Surveys were completed at the end of the visit, after participants had received their immunizations. Participants remained blinded to the agent received as they filled out their questionnaire.

Discussion

This study clearly shows the efficacy of the topical vapocoolant FM in significantly reducing immediate injection-associated pain among adult participants at an international travel clinic. Although the pain was similarly perceived at 5 min, the hypothesized point of pain
reduction was expected to be immediate, given the pharmacodynamics of topical vapocoolants, and the pain dynamics of injection vaccines. The trend towards sustained pain reduction at 5 min supports the benefit of this intervention for travel clients. Our results show an approximate 27% reduction in pain, validating our conservative study design to power the study at the 25% difference level. The lower level of pain reduction in this study compared to prior studies may be due to differences in pain perception in adults compared to children. Pediatric studies use additional nonparticipant estimates of pain that may create differences when comparing our study to prior reports.

The survey indicates a high degree of acceptance of this intervention. Anecdotally, participants returning for subsequent travel or booster injections were not re-enrolled in the study, but many spontaneously asked for topical cold therapy for future injections. The reduction in pain with 4°C saline-wetted cotton balls was not unexpected. Original research into the threshold of pain reduction with topical vapocoolants indicates 10°C as the point at which pain reduction begins. Our findings are also consistent with previous literature indicating greater pain reduction as skin temperature approaches 0°C.

The McGill PPI pain index has been validated in numerous studies. It is able to differentiate between the discomfort felt as result of saline placebo injection, alum carrier injection and vaccines. A study by Su et al. has even indicated a measurable difference in pain between the hepatitis A vaccines VAQTA (Merck) and HAVRIX (Glaxo SmithKline, Research Triangle Park, NC). This information reinforces the validity of the use of this type of pain scale.

A randomized control trial of the new combined hepatitis A and B vaccinations indicated excellent efficacy but slightly increased local pain associated with this vaccine compared to hepatitis B vaccination alone. These data, and the general trend towards combination vaccines, make the use of a pain-reducing agent attractive to enhance acceptance.

Development of the reliable, non-injection-based transdermal topical anesthetic EMLA (Eutectic Mixture of Local Anesthetics) was an important advance in the area of injection pain reduction. The oil-in-water emulsion enhances concentration of the anesthetics, facilitating absorption and penetration. The combined inconvenience of cost (approximately US $5.00 to $7.50 per dose) and 60-min delay to onset of activity make this option poorly suited for use in the adult international travel immunization setting. This potential concern was confirmed in our survey results.

A method involving the use of a mild electric current to reduce the time to onset of action of transcutaneously applied local anesthetics was developed and termed iontophoresis. This method reduces the pain associated with some office injection procedures, but has not been studied for vaccine injections. The advantage is reduction of the onset of action to 10 min. Disadvantages include cost of the device (approximately $500), the medication cost (approximately US $5.00 to $7.50 per dose), and cumbersome application for multiple injections—a common occurrence in the travel visit setting.

Jet injection delivery devices are equivalent in producing less anxiety and immediate pain, but lead to a significant increase in delayed local soreness and edema, which lasts longer than traditional needle injection discomfort. There is also a history of rare infection transmission and blood on the nozzle surface, which is difficult to fully sterilize between vaccine recipients. Newer versions use disposable nozzles and cartridges, yet retain the relatively high cost of the device (US $500 to 3000), limiting cost-effectiveness to very high volume settings.

Some may object to any intervention for vaccine recipients, given the nearly equivalent levels of pain reduction at 5 min after vaccination. However, pain is both personal and subjective. In this and other studies where patients’ preferences have been sought, several points stand out. First, participants prefer pain reduction whenever available. Second, among the international travel clients of our study, there was a clear preference for the use of topical vapocoolant in the future, with no obvious detrimental responses. Third, cost and timelines are significant factors in determining whether a given intervention will be widely useful and accepted. Fourth, this large randomized, prospective, single-blinded and adequately powered study confirms the effectiveness of FM in this setting.

The disadvantages of vapocoolants are few. Application needs to be limited to 15 s, as longer times might produce uncomfortable local freezing of the skin. Ethyl chloride, used in older studies, is flammable. The agent of this study, FM, contains fluorocarbons. A new non-flammable, fluorocarbon-free compound is currently under development by the manufacturer. Preliminary data show a similar clinical profile to the current vapocoolant agents.

Other factors favoring the use of FM include no reported history of allergy to the active ingredients, low cost, immediate onset of action, and flexibility. Since the vaccination needs of international travel clients can only be determined after specific review of individual itineraries, it is rarely possible to determine the number of injections that a person will actually need prior to evaluation at the travel consultation. Hence, an agent such as EMLA cream, which must be applied 60 min before vaccination, is not practical for use prior to the visit. Cost-effectiveness considerations favor an agent such as FM, which can be utilized for each injection, at the exact site immediately before vaccination.
Conclusion

Immunizations represent an important part of international travel preparation. Injection-associated pain is a reason why some travelers do not obtain all the recommended vaccinations. The immediate onset of action, significant efficacy and low cost make the topical vapocoolant FM an attractive agent worthy of consideration to reduce discomfort and facilitate vaccine acceptance at international travel preparation visits. Future studies with non-fluorocarbon-containing topical vapocoolants are planned.

Acknowledgments

Fluori-Methane was supplied by Gebauer Co. for use during the study without charge to the Cleveland Clinic Foundation.

Declaration of Interests

The authors had no financial or other conflicts of interest to disclose.

References

29. Lindsay L. Assessing the safety of multidose jet injectors for the administration of vaccines. Thesis. Atlanta: Emory University, 1996.