

Effect of topical vapocoolant spray on skin test wheal, flare, and pain responses

Kirk H. Waibel, MD,* and Rohit K. Katial, MD†

Background: Skin puncture and intradermal tests are commonly used to evaluate allergic rhinitis. Ethyl chloride, a topical vapocoolant spray, provides skin analgesia before venipuncture, but it has not been studied with allergy skin testing.

Objective: To determine the effects of ethyl chloride vs placebo on skin puncture testing (SPT) and intradermal allergy testing.

Methods: We enrolled 20 healthy adults with a history of positive aeroallergen skin test results in a randomized, double-masked, placebo-controlled study. Ethyl chloride and placebo sprays were randomly placed on the upper back. Paired SPT was performed with saline, histamine, and standardized aeroallergens, including Bermuda grass, Kentucky blue grass, timothy grass, cat, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae*. Serial dilutional end-point intradermal tests were then performed using 1 standardized aeroallergen. Wheal and flare areas were outlined, scanned, and digitally measured. Participants used a 10-cm visual analog scale to record pain during skin testing.

Results: Eighteen individuals completed the study. Compared with placebo, ethyl chloride had no significant effect on histamine wheal ($P = .53$), histamine flare ($P = .39$), aeroallergen wheal ($P = .10$), or aeroallergen flare ($P = .71$) area for SPT. Serial dilutional end-point intradermal testing was similar after ethyl chloride and placebo application ($P = .75$). Mean pain scores for SPT were improved with ethyl chloride compared with paired placebo skin tests, although pain scores did not reach significance for SPT ($P = .21$) or intradermal testing ($P = .87$).

Conclusions: Ethyl chloride does not significantly reduce histamine and aeroallergen wheal and flare areas during SPT and intradermal allergy skin testing. Ethyl chloride, vs placebo, reduced pain in some individuals during skin testing, although this did not attain statistical significance.

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INTRODUCTION

Allergic rhinitis is a common condition that affects 10% to 25% of the population worldwide.¹ One of the diagnostic criteria is the demonstration of allergen specific IgE, typically identified via skin testing. Allergy skin testing is tolerated well by most individuals, but it can be painful in some children and adults. Currently, there are no topical anesthetics recommended for reducing pain during allergy skin testing. Topical anesthetic creams, such as eutectic mixture of local anesthetics (EMLA; AstraZeneca LP, Wilmington, DE), have been shown to lessen pain with skin testing; however, such products also reduce the aeroallergen flare response 21% to 52%.^{2–4} Ethyl chloride (Gebauer, Cleveland, OH) is a topical vapocoolant spray currently approved for topical anesthesia in minor surgical procedures, minor sports injuries, preinjection anesthesia, and myofascial pain.⁵ This study was designed to evaluate the effects of ethyl chloride on wheal and flare responses during allergy skin testing.

METHODS

Participants

Twenty adults aged 18 to 60 years were recruited from the Allergy/Immunology Clinic at Dwight D. Eisenhower Army Medical Center (Fort Gordon, GA). Inclusion criteria included previous skin puncture test (SPT) results demonstrating a histamine wheal 3 mm or greater than the saline control and a standardized aeroallergen skin test wheal 5 mm or greater and flare 10 mm or greater. Participants were excluded if they had a history of ethyl chloride allergy, were taking oral corticosteroids, had been skin tested on the back in the previous month, were unable to stop taking all antihistamines for 7 half-lives, had a history of dermatographism, had active skin disease, were pregnant, or had asthma with a forced expiratory volume in 1 second–forced vital capacity ratio of less than 0.7. No participants were undergoing allergen immunotherapy. The study was conducted between October 21, 2003, and March 11, 2004. The Dwight D. Eisenhower Army Medical Center institutional review board approved the study, and all the participants provided written informed consent.

Allergen Tests

All SPT and intradermal testing was performed by a single-masked investigator (K.H.W.) on the upper back, with 5 cm between each skin test. One side of the back was tested at a time using 1 of 2 randomized sprays: ethyl chloride or placebo. Ethyl chloride and placebo (70% isopropyl rubbing

* Allergy and Immunology Service, Department of Medicine, Dwight D. Eisenhower Army Medical Center, Fort Gordon, Georgia.

† Division of Allergy and Immunology, National Jewish Medical and Research Center, Denver, Colorado.

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Table 1. Clinical and Subjective Outcomes of the 18 Participants Who Completed the Study*

	Placebo	Chloroethane	95% CI†	P value‡
SPT histamine area, cm ²				
Wheal	0.27 ± 0.11	0.29 ± 0.08	−0.04 to 0.08	.53
Flare	3.64 ± 2.33	3.27 ± 1.48	−1.20 to 0.46	.39
SPT aeroallergen area, cm ²				
Wheal	1.08 ± 0.73	0.95 ± 0.69	−0.30 to 0.02	.10
Flare	9.28 ± 6.06	9.13 ± 5.38	−1.23 to 0.93	.71
VAS score				
SPT	5.5 ± 2.8	5.1 ± 2.9	NA	.21
Intradermal testing	5.7 ± 2.5	5.7 ± 2.3	NA	.87
Spray sensation	4.0 ± 1.9	5.0 ± 2.4	NA	.06

Abbreviations: CI, confidence interval; NA, not applicable; SPT, skin puncture testing; VAS, visual analog scale.

* Values are given as mean ± SD.

† For the mean differences between placebo and chloroethane.

‡ Comparison of placebo and chloroethane sprays.

alcohol; Humco, Texarkana, TX) sprays were administered by a single experienced allergy technician. Ethyl chloride was applied per package recommendations (ie, for 3–7 seconds at a distance of 3–9 inches, just until the skin began to frost, then wiping the target area with an antiseptic). Placebo spray was applied for the same time and at the same distance on the other side of the back using a commercial mist sprayer that mimicked the ethyl chloride spray. After spray application, each site was wiped first with a 4 × 4-inch gauze pad moistened with isopropyl alcohol and then again with a dry 4 × 4-inch gauze pad. Skin tests were performed within 5 to 10 seconds of spray application.

All SPTs were performed using the GreerPick (Greer Laboratories, Lenoir, NC) by pressing the skin at a 90° angle. The SPTs for each participant included a negative saline control, a positive control (1 mg/mL of histamine; ALK Laboratories Inc, Wallingford, CT), and up to 6 standardized allergens: Bermuda grass (10,000 BAU/mL), Kentucky blue grass (10,000 BAU/mL), timothy grass (10,000 BAU/mL), cat (10,000 BAU/mL), *Dermatophagoides pteronyssinus* (5,000 AU/mL), and *Dermatophagoides farinae* (5,000 AU/mL) (ALK Laboratories Inc).

Once SPTs were complete, intradermal tests were performed. A separate area of the upper back was sprayed in a similar manner as described previously herein. A negative intradermal control (0.3% human serum albumin) and serial 10-fold dilutions, beginning with 1 standardized intradermal aeroallergen diluted to 1×10^{-8} of the skin puncture concentration, were placed. Intradermal skin tests were applied using a 27-gauge needle, injecting 0.03 mL to form a small bleb just beneath the skin. The intradermal allergen used was randomly selected based on the aeroallergens used during SPT.

Pain was evaluated using a 10-cm visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst pain).⁶ Participants placed a vertical line on a separate, unmarked VAS for each SPT and intradermal test. Patient sensation to placebo

and ethyl chloride was also measured once before SPT and intradermal testing using a 10-cm VAS, with 0 indicating pleasant; 5, no feeling; and 10, unpleasant.

Skin Test Tracing

Skin puncture and intradermal test results were assessed at 15 and 20 minutes, respectively. The outside border of each wheal and flare response was traced using a 0.2-mm permanent marker (Sharpie Ultra Fine; Sanford, Bellwood, IL). Traced wheal and flare responses were transferred to paper,⁷ digitally scanned (HP ScanJet 5200C; Hewlett-Packard Co, Palo Alto, Calif), and measured using a software program (ImageJ v1.24; Wayne Rasband, Research Services, National Institute of Mental Health, Bethesda, MD). This software has been determined to have a low coefficient of variation (0.19%–1.67%), with repeated measurements of areas ranging from 0.07 to 20 cm², consistent with other studies.⁷ All wheal and flare areas determined using ImageJ software were completed by a single investigator (K.H.W.) before breaking the study code.

Sample Size

Based on findings from 2 studies^{8,9} that evaluated the GreerPick, this device can produce wheal and flare measurements that vary up to 30% with repeated testing. Previous studies^{2–4} that measured the effect of EMLA did not provide a power analysis or a discussion regarding the variability of the skin test device. Using these studies and the variability of the GreerPick skin test device, we estimated that 18 individuals were required to detect a 30% difference for wheal and flare area after ethyl chloride and placebo application, powered to 0.8.

Statistical Methods

Data are presented as mean ± SD. Histamine wheal and flare areas were compared using a paired *t* test because each participant had a single histamine SPT for each spray. Mean aeroallergen wheal area, aeroallergen flare area, and VAS

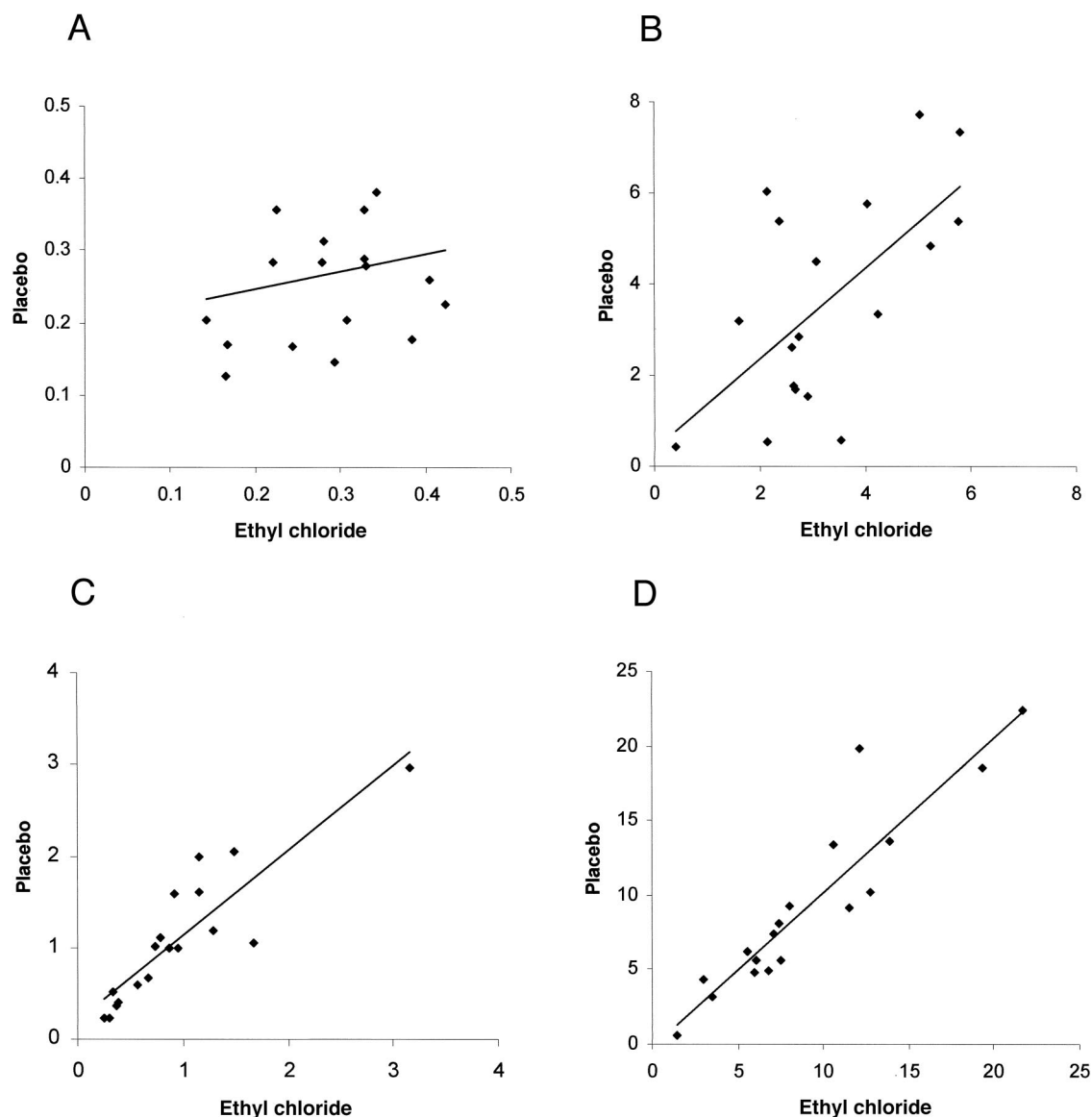


Figure 1. Scatterplots showing wheal and flare area measurements. Points represent relationships between mean areas (in cubic centimeters) for paired skin tests with ethyl chloride and placebo for histamine wheal ($r = 0.18$; $P = .53$) (A), histamine flare ($r = 0.63$; $P = .39$) (B), aeroallergen wheal ($r = 0.88$; $P = .10$) (C), and aeroallergen flare ($r = 0.92$; $P = .71$) (D).

scores for participants were compared using the Wilcoxon test. χ^2 Tests were used to determine whether the aeroallergen flare extinction during end-point intradermal tests occurred at the same dilution after ethyl chloride compared with placebo. $P < .05$ was considered statistically significant.

RESULTS

Of 20 individuals enrolled, 18 completed the study. Their mean age was 35 years; 55% of participants were men, 55% were white, and 33% had a history of asthma. One participant did not complete the intradermal portion of the study and was not included in the analysis. Another participant had a posi-

tive SPT reaction to timothy grass and cat 1 year earlier but negative results at the time of study entry.

Eighteen histamine tests and 49 aeroallergen skin tests, including 8 with Bermuda grass, 8 with Kentucky blue grass, 9 with timothy grass, 8 with cat, 8 with *D pteronyssinus*, and 8 with *D farinae*, were performed. The median number of aeroallergen SPTs for participants was 2.5 (range, 1–6). Compared with placebo, mean histamine wheal, histamine flare, aeroallergen wheal, and aeroallergen flare areas after ethyl chloride were not significant (Table 1). Mean wheal and flare areas after ethyl chloride, compared with placebo, are also shown for each participant (Fig 1). Mean wheal and flare

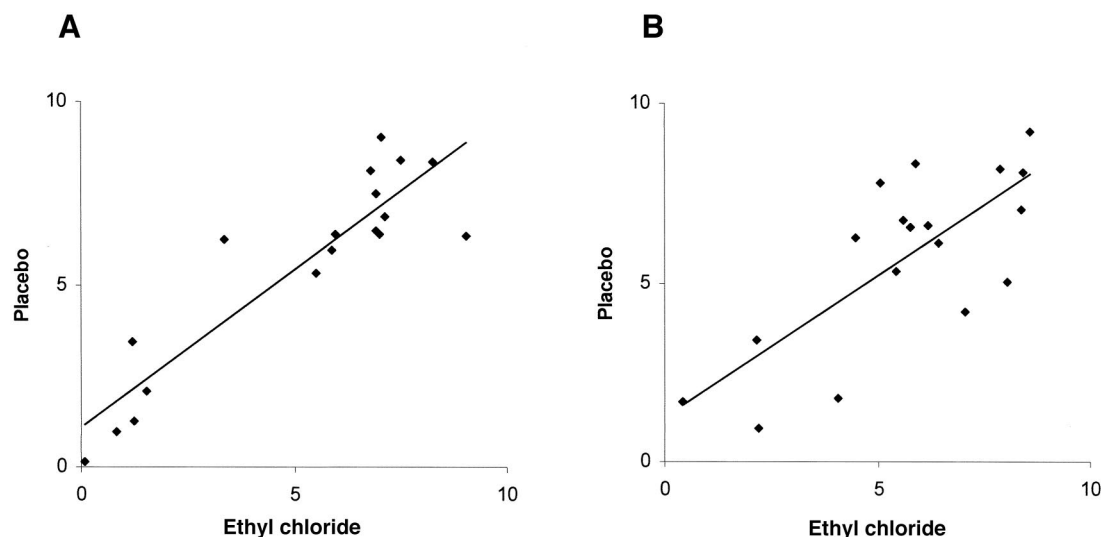


Figure 2. Scatterplots showing mean pain scores for each participant ($n = 18$). Each point represents a mean pain score after ethyl chloride and placebo during skin puncture testing ($r = 0.91$; $P = .21$) (A) and intradermal testing ($r = 0.75$; $P = .87$) (B). The pain scale ranged from 0 (no pain) to 10 (worst pain).

areas after ethyl chloride that were less than 70% of its paired test included 2 histamine wheals (11%), 5 histamine flares (28%), 3 aeroallergen wheals (17%), and 2 aeroallergen flares (11%).

Serial end-point intradermal testing did not show a difference between ethyl chloride and placebo ($P = .75$). Standardized aeroallergens used for intradermal testing included Bermuda grass ($n = 5$), Kentucky blue grass ($n = 1$), timothy grass ($n = 1$), *D pteronyssinus* ($n = 5$), *D farinae* ($n = 3$), and cat ($n = 3$). The median for the intradermal dilution resulting in flare extinction was 1×10^{-7} (range, 1×10^{-2} to 1×10^{-9}) of the skin puncture concentration. Sixteen of 18 participants had the same dilution for flare extinction after ethyl chloride and placebo, and 2 had flare extinction at 1 lower dilution with ethyl chloride compared with placebo.

Pain responses during SPTs ranged across the entire VAS and did not differ significantly. Mean $\pm$ SD pain scores after placebo and ethyl chloride for SPTs were 5.5 ± 2.8 and 5.1 ± 2.9 , respectively ($P = .21$) (Fig 2A). Mean $\pm$ SD pain responses for intradermal testing were 5.7 ± 2.5 after placebo and 5.7 ± 2.3 after ethyl chloride ($P = .87$) (Table 1 and Fig 2B). Pain scores did not significantly change depending on the order of ethyl chloride application. Finally, participants scored the placebo spray sensation as more "pleasant" than ethyl chloride, although this did not reach significance ($P = .06$) (Table 1).

DISCUSSION

The American Academy of Pediatrics recommends that pediatric subspecialists identify and address procedure-related pain.¹⁰ Most individuals tolerate skin testing without difficulty, although some individuals may experience substantial discomfort or pain. A common topical anesthetic, EMLA, has significantly reduced or eliminated the flare response, an

important aspect of skin test interpretation.²⁻⁴ Furthermore, EMLA can be limited by cost (\$7.50 per application), onset time (60–120 minutes), and the risk of precipitating methemoglobinemia.⁵ Ethyl chloride briefly cools the area sprayed to approximately -20°C , is inexpensive (\$0.50 per application), can be rapidly applied (seconds), and has an immediate onset of action.^{5,11} More serious adverse effects, such as frostbite,¹² contact dermatitis,¹³ and death,¹⁴ have been reported but occurred with inhalation or prolonged exposure.

In this study, ethyl chloride did not significantly affect wheal and flare responses to either histamine or standardized aeroallergens. Furthermore, no SPT flare response was extinguished after ethyl chloride application, a finding observed with EMLA cream.² Serial intradermal end-point testing demonstrated that flare extinction occurred at the same dilution for ethyl chloride and placebo. This finding suggests that some of the variability observed between ethyl chloride and placebo for SPTs may have resulted from the variability of the skin testing device rather than as a direct effect of ethyl chloride.

One negative finding of this study is the lack of significant pain reduction after ethyl chloride application compared with placebo. A variety of factors may have contributed to this finding. First, this study was powered to detect a difference in wheal and flare skin test area rather than pain responses. Pain responses varied (range, 0–9.2) across the entire 10-cm VAS (Fig 2). Some individuals had minimal or no pain with placebo treatment; therefore, these individuals would likely experience little benefit regardless of the type of topical anesthetic used. Sicherer and Eggleston² demonstrated pain reduction in an adult group after EMLA, but the differences were subjectively small, improving from either "minimal pain" or "barely perceptible pain" to "pressure only." Another possibility explaining the lack of pain reduction is that

the vapocoolant effect of ethyl chloride may have dissipated before placing the skin test. Labeling information for ethyl chloride describes the cooling effect as lasting from "seconds to a minute," but the duration of this effect may have varied between individuals.

In conclusion, ethyl chloride applied immediately before skin testing did not adversely affect histamine or standardized aeroallergen wheal and flare responses in adults. Although there was a trend toward improved pain scores with ethyl chloride for SPTs, this did not reach statistical significance. Further study should be considered to determine which individuals may experience substantial pain or discomfort during allergy skin testing because these individuals are more likely to benefit from pain-reducing measures.

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Requests for reprints should be addressed to:
Kirk H. Waibel, MD
Allergy and Immunology Service
Dwight D. Eisenhower Army Medical Center
300 Hospital Rd, 8th Floor
Fort Gordon, GA 30905-5650
E-mail: kirk.waibel@se.amedd.army.mil