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Prospective, double blind, randomized, controlled trial comparing vapocoolant spray versus placebo spray in adults undergoing intravenous cannulation☆

Sharon E. Mace[a,b,*]

[a] Professor of Medicine, Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Faculty MetroHealth Medical Center/Cleveland Clinic Emergency Medicine Residency, Cleveland, OH, United States
[b] Director of Research Cleveland Clinic Emergency Services Institute, Cleveland Clinic, 9500 Euclid Ave, E-19, Cleveland, OH 44195, United States

HIGHLIGHTS

- Vapocoolant spray significantly decreased the pain of intravenous cannulation.
- There were no complications or adverse events.
- Minor side effects that occurred in a few patients resolved quickly.
- No visible skin abnormalities were present 5–10 min after spray application.

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ABSTRACT

Objectives: Painful diagnostic and therapeutic procedures are common in the health care setting. Eliminating, or at least, minimizing the pain associated with various procedures should be a priority. Although there are many benefits of providing local/topical anesthesia prior to performing painful procedures, ranging from greater patient/family satisfaction to increased procedural success rates; local/topical anesthetics are frequently not used. Reasons include the need for a needlestick to administer local anesthetics such as lidocaine and the long onset for topical anesthetics. Vapocoolants eliminate the risks associated with needlesticks, avoids the tissue distortion with intradermal local anesthetics, eliminates needlestick pain, have a quick almost instantaneous onset, are easy to apply, require no skills or devices to apply, are convenient, and inexpensive. The aims of this study were to ascertain if peripheral intravenous (PIV) cannulation pain would be significantly decreased by using a vapocoolant (V) versus sterile water placebo (S) spray, as determined by a reduction of at least ≥1.8 points on numerical rating scale (NRS) after vapocoolant versus placebo spray, the side effects and incidence of side effects from a vapocoolant spray; and whether there were any long term visible skin abnormalities associated with the use of a vapocoolant spray.
Materials and methods: Prospective, randomized, double-blind controlled trial of 300 adults (ages 18–80) requiring PIV placement in a hospital ED, randomized to S ($N = 150$) or V ($N = 150$) prior to PIV. Efficacy outcome was the difference in PIV pain: NRS from 0 (none) to worst (10). Safety outcomes included a skin checklist for local adverse effects (i.e., redness, blanching, edema, ecchymosis, itching, changes in skin pigmentation), vital sign (VS) changes, and before/after photographs of the PIV site.
Results: Patient demographics (age, gender, race), comorbidity, medications, and vital signs; and PIV procedure variables (e.g., IV needle size, location, number of IV attempts, type and experience of healthcare provider performing the IV) were not significantly different for the two groups. Median (interquartile range) PIV pain was 4 (2, 7) (S) and 2 (0, 4) (V) ($P < 0.001$). Skin checklist revealed minimal erythema: S 0% ($N = 0/150$), V: 2.7% (4/150), which resolved within 5 min, and no blanching, skin pigmentation changes,

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* Corresponding author at: Department of Emergency Medicine, Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Faculty MetroHealth Medical Center/Cleveland Clinic Emergency Medicine Residency, Cleveland, OH, United States.
E-mail address: maces@ccf.org

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itching, edema, or ecchymosis. Photographs at 5–10 min revealed no visible skin changes in any patient ($N = 300$), vapocoolant ($N = 150$) or placebo groups ($N = 150$). Complaints ($N = 26$) were coolness/cold feeling S 8.7% ($N = 13$), V 7.3% ($N = 11$), coolness/numbness S 0% ($N = 0$), V 0.7% ($N = 1$), and burning S 0.7% ($N = 1$), V 0 (0%). Patient acceptance of the vapocoolant spray was high: 82% (123/150) of the patients stated they would use the spray in the future, while only 40.7% (61/150) of the placebo group stated they would use the placebo spray in the future.

Conclusions and Implications: Vapocoolant spray significantly decreased peripheral intravenous cannulation pain in adults versus placebo spray and was well tolerated with minor adverse effects that resolved quickly. There were no significant differences in vital signs and no visible skin changes documented by photographs taken within 5–10 min postspray/PIV.

1. Introduction

Painful diagnostic and therapeutic procedures are frequently performed in the emergency department (ED) [1,2]. Suboptimal pain management or oligoanesthesia has been noted as "a problem for emergency medicine" [3]. Failure to adequately treat pain has significant short-term and long-term consequences [4,5]. This oligoanesthesia [6–8] extends to painful procedures [9–11]. Health care providers frequently fail to provide adequate anesthesia prior to painful procedures even when patients and families indicate that they would like to receive analgesia before painful procedures including needlestick procedures [1,9–13].

Benefits of adequate analgesia include increased patient/family satisfaction and increased procedural success [6,14–16]. Yet topical anesthesia prior to procedures is underused [10,11,14].

Topical skin refrigerants, or vapocoolants, have some advantages over other options for local anesthesia including eliminates the risk of needlestick injury, avoids tissue distortion, avoids the pain of intradermal anesthetics, rapid almost instantaneous onset (some topical analgesic creams take up to an hour to achieve clinically significant pain relief), easy to apply, no need for devices for administration (which have been associated with delayed local soreness and edema), less administration time, greater staff convenience, decreased ED length of stay, and is inexpensive [1,5,10,17–21].

This study sought to determine the efficacy and safety of a vapocoolant spray in adults undergoing peripheral intravenous cannulation (PIV). We hypothesized that pain of PIV would be at least 1.8 points lower after vapocoolant spray compared to placebo spray and that there would be no permanent visible changes associated with the use of a vapocoolant spray [22,23].

2. Materials and methods

Thus study, termed IMPACT PAIN II for "IMproved PAtient Comfort Trial: Pain Assessment in Intravenous CaNnulation" was an investigator-initiated study supported by a research grant from the Gebauer Company. The sponsor had no involvement in the study other than funding and supplying the spray cans used for the administration of the placebo spray and the vapocoolant spray.

2.1. Study design and setting

This was a prospective, double blind, randomized controlled efficacy and safety trial conducted at an urban, academic, tertiary care referral hospital conducted from August 2012 to December 2014. The study was approved by the institutional review board and all patients gave written informed consent.

2.2. Study population

Adults (ages 18–80 years) undergoing peripheral intravenous cannulation (PIV) in the ED were eligible for enrollment in the study. Inclusion criteria were: patient undergoing PIV, mentally competent patient able to understand the consent form, and clinically stable. Patients were excluded from the study if any of the following criteria were met: allergy to the spray components (e.g. 1,1,1,3,3-pentafluoropropane or 1,1,1,2-tetrafluoroethane), critically ill or unstable, extremes of age (pediatric < 18 years or elderly geriatric > 80 years), pregnant, previous experience with any vapocoolant spray, PIV site located in area of compromised blood supply, PIV site located in area of insensitive skin, patient intolerant of cold or with hypersensitivity to cold, and patient unwilling to give consent. Examples of PIV sites located in areas of compromised blood supply would include patients with peripheral vascular disease, gangrene, Raynaud's disease or Buerger's disease. Examples of patients with insensate or abnormal sensation of the skin would include patients with a peripheral neuropathy. None of the patients recently received an analgesic (such as an opioid) prior to the venipuncture. Informed written consent was obtained from all subjects.

This was a convenience sample since patients were enrolled when the ED research staff was available, e.g. day and evening shifts on weekdays and weekends. The ED research staff members conducting the study were not involved in the care of the patient or in starting the PIV line. The primary researcher was not present and not involved in patient enrollment or data analysis. A research assistant approached the patient if the patient was in the appropriate age range (18–80 years) and if the patient was clinically stable (e.g. not in shock or respiratory distress or had no alteration of mental status), and obtained informed written consent.

The past medical history including comorbidities, current medications and characteristics of the PIV itself were listed in order to determine if the patient populations for the two groups were well matched at baseline since comorbidity and medication use, and the PIV itself could possibility affect the difficulty of the PIV procedure and the response to the pain of the PIV.

Patients were randomized to either sterile water placebo spray (Nature's Tears®) or to vapocoolant spray (1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane) (Gebauer's Pain Ease® Medium Stream). The application of the spray in all patients was completed by one of two trained research assistants whose job was to enroll patients and to standardize administration of the topical spray. After prepping and cleansing the PIV site, the spray was applied in the same manner for all patients, both placebo and vapocoolant subjects, as recommended by the manufacturer. The specific technique of spray application for both the placebo spray and the vapocoolant spray was: hold the can 3–7 in from the PIV site, spray onto the PIV site steadily 4–10 s or until the skin begins turning white, whichever comes first (the anesthetic

effect is complete at this time), then, immediately perform the IV needlestick for the IV line. There is about a one minute time frame to complete the PIV cannulation since the topical anesthetic lasts only about one minute.

The spray cans were not identified as to whether they were the placebo spray or the vapocoolant spray and thus, were blinded to both the subjects, the research assistants applying the spray and the health care providers performing the PIV. The actual PIV was done by the ED staff and not by the two research associates.

Randomization was accomplished utilizing a computer random number generator with block randomization using randomly varied block sizes of 20 or 30. The spray cans were supplied from outside the ED in varied block sizes such that the randomization was not done by or knowledgeable to the ED research staff performing the actual patient enrollment and data collection in order to maintain allocation concealment.

2.3. Data collection and processing

All data was collected by trained research associates who had no patient care duties. Their research duties included patient enrollment, data recording and application of the spray. They recorded on standardized case report forms: the demographics, PIV procedural data, vital signs (completed by ED nursing staff), clinical variables (from the electronic medical record), all side effects/complications, and pain scales (e.g. numeric rating scale [NRS]) as reported by the patients: NRS immediately post spray/pre PIV cannulation, and NRS for the pain of PIV cannulation. They completed the standardized checklist and took before and after photographs of the IV site to document any visible skin changes.

All data was entered into a REDCap database and then analyzed using R software (version 3.1.1) by a biostatistician. Continuous variables were summarized using means with variability assessed using standard deviations. Categorical variables were summarized as counts and percentages. Tests for differences of continuous variables were done using Welch 2-sample *t*-tests or Wilcoxon's rank-sum tests. Tests on categorical variables were done using either Pearson's chi-squared tests with Yates continuity correction or Fisher's exact test for count data. Significance was at $P < 0.05$ and the results of testing were given by *P*-values and/or confidence intervals.

2.4. Outcome measures

The primary efficacy outcome was the pain of PIV on a verbal NRS scale ranging from 0 (none) to 10 (worst). The primary safety measures were the documentation of any and all adverse effects/complications and vital signs. Secondary safety measures included a skin checklist for any changes (rated none, mild, moderate, severe) of the skin: redness, blanching or pallor, changes in skin pigmentation, itching, edema, or other (such as ecchymosis) done immediately post spay, NRS post spray/pre PIV, and photographs of the PIV site done pre and 5–10 min post application of the spray/post PIV for any visible skin changes.

According to previous studies, a change in NRS of 1.3 or greater is deemed clinically significant [22,23], while a previous pediatric IV study found a difference of 18 on a 0–100 mm VAS scale between placebo vs. vapocoolant spray [16]. Therefore, we decided to use a decrease of $\geq$1.8 on the NRS since this would include the meaningful difference. To detect a decrease of 1.8 on the NRS, a sample size of 277 was chosen, assuming a 2-tailed test, power of 80%, and type I error rate of 0.05. The sample size was increased to 300 (150 per group) to compensate for potential dropouts or protocol deviations.

3. Results

3.1. Study subjects

Of the 544 patients recruited to the study, 300 consented, were randomized and received their allocated treatment: 150 patients received sterile water spray (placebo arm) and 150 patients received vapocoolant spray (treatment arm) (Fig. 1). For all 300 study subjects, the mean age (±SD) was 42.8 (±16.6) years (range 18–80 years), with 120 males and 180 females: 150 African-Americans, 137 Caucasians, and 13 other. The patients in the two study arms had similar baseline characteristics with no significant differences in any of the demographic variables (age, gender, race); or clinical characteristics (comorbidities, or medications) (Table 1). The characteristics of the PIV itself were similar between the two groups with no significant differences in PIV location, PIV needle gauge, PIV success rate, number of PIV attempts, difficulty of PIV, or with the health care providers performing the PIV (years' experience and role in ED) except for spray time: 7.5 (V) vs. 10 s (S). The procedure (e.g. PIV) was performed in <1 min in all patients (Table 2).

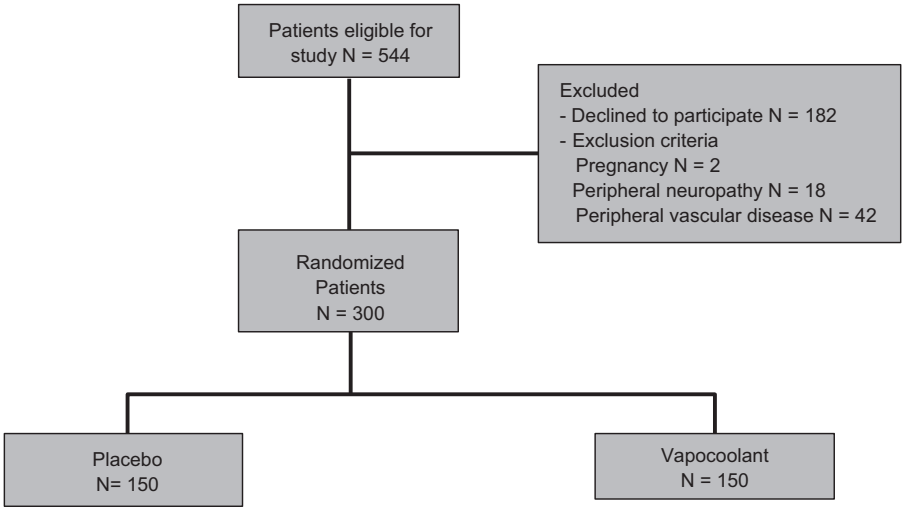

Fig. 1. Participant flow diagram according to the consolidated standards of reporting trial guidelines.

Table 1
Patient demographics, clinical variables, vital signs.

	Placebo saline spray (*N* = 150 patients)	Vapocoolant spray (*N* = 150 patients)	*P*-value	All patients (*N* = 300 patients)
Demographics				
Age (years): mean (±SD)	42.7 (± 16.6)	43.0 (± 16.6)	0.91	42.8 (±16.6)
Gender: number of patients (%)	Male 64 (42.7%) Female 86 (57.3%)	Male 56 (37.3%) Female 94 (62.7%)	0.41	Male 120 (40%) Female 180 (60%)
Race: number of patients (%)	African-American 73 (48.7%) Caucasian 68 (45.3%) Other 9 (6%)	African-American 77 (51.3%) Caucasian 69 (46.0%) Other 4 (2.7%)	>0.99	African-American 150 (50%) Caucasian 137 (45.7%) Other 13 (4.3%)
Comorbidity				
Hypertension	65 (43.3%)	65 (43.3%)	>0.99	130 (43.3%)
Diabetes	35 (23.3%)	34 (22.7%)	>0.99	69 (23%)
COPD	11 (7.3%)	11 (7.3%)	>0.99	22 (7.3%)
Cancer	22 (14.7%)	20 (13.3%)	0.87	42 (14.3%)
Current chemotherapy	4 (2.7%)	2 (1.3%)	0.68	6 (2%)
Past chemotherapy	5 (3.33%)	3 (2%)	0.72	8 (2.7%)
Current radiation therapy	0 (0%)	2 (1.3%)	0.67	2 (1%)
Past radiation therapy	6 (4%)	3 (2%)	0.50	9 (3%)
Status post mastectomy	1 (0.7%)	4 (2.7%)	0.37	5 (1.7%)
Obesity	21 (14%)	35 (23.3%)	0.54	56 (18.7%)
Renal disease	5 (3.3%)	7 (4.7%)	0.77	12 (4%)
Hemodialysis	4 (2.7%)	3 (2%)	>0.99	7 (2.3%)
Sickle cell disease	2 (1.3%)	1 (0.7%)	>0.99	3 (1%)
Grave's disease	0 (0%)	1 (0.7%)	> 0.99	1 (0.3%)
Gout	6 (4%)	8 (5.3%)	0.78	14 (4.7%)
Osteoarthritis	9 (6%)	11 (7.3%)	0.82	20 (6.7%)
Rheumatoid arthritis	5 (3.3%)	7 (4.7%)	0.77	12 (4%)
Systemic lupus erythromatosis	6 (4.0%)	1 (0.7%)	0.13	7 (2.3%)
Sarcoidosis	1 (0.7%)	0 (0%)	>0.99	1 (0.3%)
Scleroderma	1 (0.7%)	0 (0%)	>0.99	1 (0.3%)
Polymyositis	1 (0.7%)	0 (0%)	>0.99	1 (0.3%)
Spondyloarthropathy	1 (0.7%)	1 (0.7%)	>0.99	2 (0.7%)
Other rheumatologic disorders	2 (1.3%)	3 (2%)	>0.99	5 (1.7%)
GI disorders: Crohn's	1 (0.7%)	1 (0.7%)	>0.99	2 (0.7%)
GI disorders: celiac disease	1 (0.7%)	0 (0%)	>0.99	1 (0.3%)
Multiple sclerosis	2 (1.3%)	1 (0.7%)	>0.99	3 (1%)
History of blood clot in upper extremity	4 (2.7%)	4 (2.7%)	>0.99	4 (2.7%)
IV drug use	3 (2%)	0 (0%)	0.25	3 (1%)
Dehydration in last 72 h	23 (15.3%)	26 (17.3%)	0.75	49 (16.3%)
Surgery in last 30 days	9 (6%)	13 (8.7%)	0.51	22 (7.3%)
Medications				
Acetaminophen	18 (12%)	18 (12%)	>0.99	36 (12%)
Opioids (acetaminophen-oxycodone or acetaminophen-hydrocodone)	34 (22.7%)	33 (22%)	>0.99	67 (22.3%)
Nonsteroidal anti-inflammatory drugs (NSAIDS)	25 (16.7%)	28 (18.7%)	0.76	53 (17.7%)
Anticonvulsants	17 (11.3%)	12 (8%)	0.43	29 (9.7%)
Antidepressants	14 (9.3%)	18 (12%)	0.57	32 (10.7%)
Benzodiazepines	13 (8.7%)	10 (6.7%)	0.66	23 (7.7%)
Corticosteroids (e.g. prednisone)	9 (6%)	9 (6%)	>0.99	9 (6%)
Vital signs				
Blood pressure: systolic (mm Hg), mean (±SD)	139.1 (±24.0)	135.7 (±21.9)	0.20	137.4 (±23.0)
Blood pressure: diastolic (mm Hg), mean (±SD)	80.0 (±15.0)	78.0 (±15.3)	0.26	79.0 (±15.2)
Heart rate (beats/min)	84.5 (±15.8)	85.7 (±16.4)	0.52	85.1 (±16.1)
Respiratory rate (breaths/min)	18.0 (±1.9)	18.3 (±2.6)	0.29	18.2 (±2.3)

3.2. Results: efficacy

The median NRS interquartile range (IQR) for PIV cannulation pain was 4 (2–7) for the placebo spray group vs. 2 (0–4) for the vapocoolant spray group ($P < 0.001$) (Fig. 2). Over one-third (35% = 52/150) of the patients in the vapocoolant group reported no pain (NRS = 0) for their IV start compared with 8.7% (13/150) for the placebo group ($P < 0.001$) (Fig. 3).

3.3. Results: safety

There were no significant differences in vital signs between the two groups (Table 1). There were 26 complaints (Table 3). In the placebo group, 13 (8.7%) complained of coolness/cold feeling, and 1 (0.7%) had burning at the site. In the vapocoolant group, 11 (7.3%) complained of coolness/cold feeling and 1 (0.7%) complained of coolness and numbness. There were no serious side effects/adverse

Table 2
Characteristics of the peripheral intravenous cannulation procedure.

	Placebo spray (*N* = 150 patients)	Vapocoolant spray (*N* = 150 patients)	*P*-value	All patients (*N* = 300 patients)
Needle size			0.20	
18 gauge	39 (26%)	35 (23.3%)		74 (24.7%)
20 gauge	100 (66.7%)	103 (68.7%)		203 (67.6%)
22 gauge	11 (7.3%)	12 (8%)		23 (7.7%)
Location of PIV			0.16	
Hand	5 (3.3%)	8 (5.3%)		13 (4.3%)
Antecubital fossa	88 (58.6%)	94 (62.7%)		182 (61%)
Forearm	50 (33.3%)	44 (29.3%)		94 (31.3%)
Wrist	7 (4.7%)	4 (2.7%)		11 (3.7%)
Total number of PIV attempts			0.58	
One	114 (76%)	124 (82.7%)		238 (79.3%)
Two	27 (18%)	17 (11.3%)		44 (14.7%)
Three	5 (3.3%)	7 (4.7%)		12 (4%)
Four	4 (2.7%)	1 (0.7%)		5 (1.7%)
Five	0 (0%)	1 (0.7%)		1 (0.3%)
Job description of healthcare provider starting the PIV			0.97	
Paramedic	91 (60.7%)	89 (59.3%)		179 (59.7%)
Registered nurse	58 (38.7%)	60 (40%)		117 (39%)
Licensed practical nurse	1 (0.7%)	1 (0.7%)		2 (0.7%)
Number years experience of individual performing the PIV, mean ± SD [95% CI]		[95% CI]	0.83	[95% CI]
0–2 years	13 (8.7%)	11 (7.3%)		24 (8%)
3–5 years	34 (23.3%)	38 (25.3%)		72 (24%)
5–10 years	47 (31.3%)	51 (34%)		99 (33%)
10+ years	56 (37.3%)	50 (33.3%)		106 (35.3%)
Patient question				
Would you use this spray for future IVs?	61 (49.7%)	123 (82%)	<0.001	184 (61.3%)
Spray time seconds median [P25, P75]	10 [8,10]	7.5 [6,10]	<0.001	10 [7,10]

Table 3
Patient comments: side effects.

Side effect	Placebo spray (*N* = 150)	Vapocoolant spray (*N* = 150)	*P*-value
Coolness/cold feeling	13 (8.7%)	11 (7.3%)	0.63
Coolness and numbness	0 (0%)	1 (0.7%)	>0.99
Burning	1 (0.7%)	0 (0%)	>0.99
No comment	136 (90.7%)	138 (92%)	>0.99

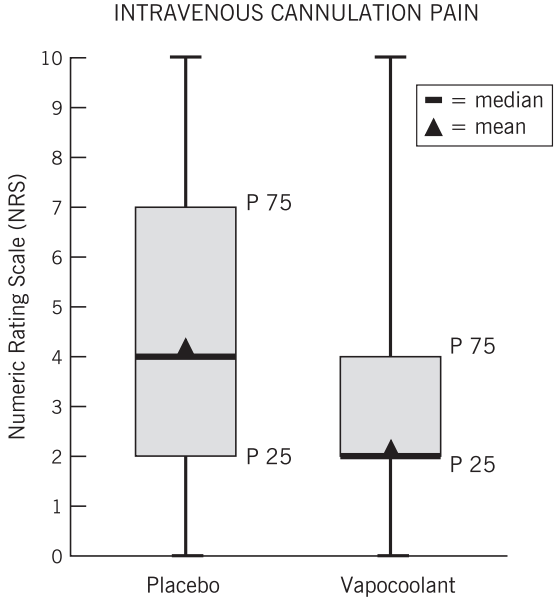

Fig. 2. The pain of peripheral intravenous cannulation (PIV) on numeric rating scale (NRS): box and whisker plots of NRS for the placebo spray and the vapocoolant spray. The median is the center line, the boxes are the 25th to 75th percentile and the triangle is the mean.

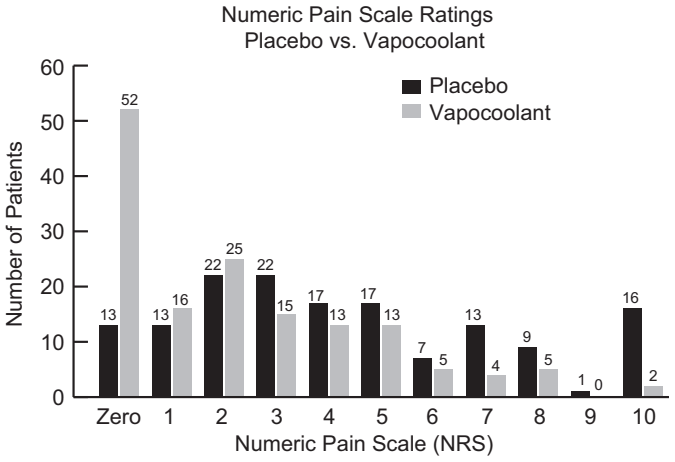

Fig. 3. Frequencies of the numeric rating scale (NRS) for the placebo spray and the vapocoolant spray for all the points (0 to 10) on the NRS.

events or complications and minor adverse effects, such as redness of the skin, resolved in <5 min.

The skin checklist completed immediately post spray revealed minimal redness in 4 patients in the vapocoolant group (4/150 = 2.7%), which resolved within 5 min post spray application/post PIV and no redness in the saline placebo group. There

Table 4
Skin checklist: immediately postspray.

	Placebo spray ($N = 150$ patients)	Vapocoolant spray ($N = 150$ patients)	P-value
Redness			0.13
None	150	146 (97.3%)	
Minimal	0	4 (2.7%)	
Moderate	0	0	
Severe	0	0	
Blanching			
None	150	150	>0.99
Minimal	0	0	
Moderate	0	0	
Severe	0	0	
Changes in skin pigmentation			
None	150	150	>0.99
Mild	0	0	
Moderate	0	0	
Severe	0	0	
Itching			
None	150	150	>0.99
Mild	0	0	
Moderate	0	0	
Severe	0	0	
Edema			
None	150	150	>0.99
Mild	0	0	
Moderate	0	0	
Severe	0	0	
Other			>0.99
None	0	0	
Mild	0	0	
Moderate	0	0	
Severe	0	0	

was no blanching, skin pigmentation changes, itching, edema, bruising, or other visible skin changes reported for either group (Table 4).

Immediately post spray/pre PIV cannulation, the median NRS was the same for the placebo spray and for the vapocoolant spray at 0 and the IQR was between 0 and 0 for the placebo spray and 0 and 2 for the vapocoolant spray ($P < 0.001$). Patients were asked "Would you want to use this spray for future IVs?" Of the vapocoolant group, 82% (123/150) responded affirmatively versus 40.7% (61/150) of the placebo group ($P < 0.001$) (Table 2). Before-and-after photographs of the spray/PIV site revealed no visible skin changes in any of the patients no matter what the gender, ethnicity, or age and no matter whether they received the placebo or vapocoolant spray.

4. Discussion

Painful diagnostic and therapeutic medical procedures, especially needlestick procedures, are frequently performed in the ED [1,11,13,14]. Unfortunately, health care providers frequently fail to provide adequate analgesia prior to painful procedures, even when patients indicated that they would like to receive analgesia before painful procedures including needlestick procedures [6]. Vapocoolants, also known as topical skin refrigerants, have some advantages over other options for local anesthesia including avoids the risk of needlestick injury and the pain of the needlestick injection of intradermal local anesthetics, rapid almost instantaneous onset (some topical creams take up to an hour for effect), easy to apply (no need for devices for application) and is inexpensive. Recent evidence from both human and animal studies indicates that topical refrigerant sprays are safe, e.g. have no lasting skin abnormalities with proper application and no effect on the microcirculation [21,24].

This prospective, double-blind, randomized, placebo-controlled trial demonstrated a significant decrease in the acute pain of PIV cannulation in adult ED patients after application of topical vapocoolant spray (1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane) compared with placebo spray and safety with no visible skin abnormalities 5–10 min after spray application. Other studies have considered the issue of skin sterility with application of a vapocoolant spray and concluded there was no increased risk of infection when a topical vapocoolant spray was used [25,26]. The analgesic effect of vapocoolants is thought to be via rapid cooling [27] by decreasing "both initiation and conduction impulses in surrounding (peripheral) sensory nerve", thereby interrupting the nocioceptive input into the spinal cord and raising the pain threshold [28]. In an animal study, cryotherapy or cold therapy increases the pain threshold and decreases the nerve conduction velocity [29]. Vapocoolant sprays are thought to produce "the sensation of cooling and analgesia through activation of transient receptor potential (TRP) ion channels in cold-sensitive peripheral sensory neurons" [30].

This study is unique in several respects. This is the first large ($N = 300$) prospective, double-blind, randomized controlled trial in an ED patients, which looked at both safety and efficacy. By comparison, an earlier study that used health care provider volunteers, had a much smaller N (only 38 volunteers) and was in a non-acute care setting (healthy volunteers, not actual ED patients), used a different vapocoolant spray (e.g. ethyl chloride), and did not address the safety issue. However, they also found a decrease in pain of PIV cannulation with the use of a vapocoolant spray: verbal NRS (median, IQR) scores were placebo (sterile water spray) 4 (2–5) vs. ethyl chloride spray 2 (1–4) [31].

A study in a different age group, children (ages 6–12 years) in a Canadian pediatric ED also found a significant decrease in the pain of PIV cannulation with the use of the 1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane spray compared to a placebo saline spray: (mean difference 19 mm, 95% confidence interval [CI] 6–32 mm, $P < 0.01$) using a 100-mm color visual analogue scale. Moreover, the first attempt PIV cannulation success rate was significantly greater for the vapocoolant spray (85%) than placebo spray (62.5%) (mean difference 22.5%, 95% CI 3.2–39.9%, $P = 0.03$). The number needed to treat to prevent one cannulation failure was 5 [16].

Another smaller non-blinded Australian study using a different vapocoolant; COLD spray®; a mixture of propane, butane and pentane; in adult ED patients comparing subcutaneous lidocaine vs. COLD spray also found significantly greater PIV success rates for the COLD spray group (83.6%) vs. lidocaine group (67.3%) ($P = 0.005$) and a significantly decreased pain of PIV insertion ($P < 0.001$) with the COLD spray [19].

The pain of PIV cannulation in our trial is similar to that reported in other studies. The study from Scotland that compared 3 groups: no treatment, intradermal lidocaine and ethyl chloride for PIV cannulation on a 0–10 VAS scale in adult females undergoing outpatient gynecologic surgery found the pain of PIV insertion with no treatment was 3.8 ± 2.1 (mean $\pm$ SD) vs. ethyl chloride group 1.8 ± 1.5 (mean $\pm$ SD) ($P < 0.001$). Intradermal lidocaine also significantly decreased the pain of PIV insertion, but with significantly decreased vein visibility and decreased ease of cannulation compared to the no treatment or ethyl chloride groups ($P < 0.001$) [18]. Comparatively, the pain of PIV cannulation for our placebo group was 4.3 ± 3.0 (mean $\pm$ SD) and median (IQR) 4 (2, 7) versus the vapocoolant group 2.3 ± 2.4 (mean $\pm$ SD) and median (IQR) 2 (0, 4) (Fig. 2).

5. Limitations

This study has several limitations. Although we did include a wide age range of adults, ages 18–80 years, we did not evaluate children or "older" geriatric patients (>80 years), we evaluated only one needlestick procedure and we used one formulation of vapocoolant spray. This was done to standardize our methodology, but may limit our generalizability, although other studies suggest that our findings may be generalizable to other patient populations, other needlestick procedures, and other vapocoolant sprays [16,32–35].

Our study is consistent with the study in a pediatric ED that also found significantly decreased PIV cannulation pain and a higher PIV success rate in children with the use of a vapocoolant spray compared to a placebo spray [16]. Other research documented significantly decreased pain for various other needlestick procedures including immunizations in both children [32] and in adults [15,33] and as a pre-injection anesthetic [34,35]. These studies [15,16,32–35] used the same formulation, 1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane, of vapocoolant spray that we used in our clinical trial. Studies using other vapocoolant sprays e.g. ethyl chloride, or a propane/butane/pentane blend, have also found that these formulations decrease needlestick pain in adults [18,19,36–38].

In these studies and our study, the proper application of the vapocoolant spray as described in the methodology was followed. The importance of appropriate spray application: adequate spray time, proper height or distance from the site, etc. cannot be overlooked [28]. A few studies that found conflicting results failed to adhere to the recommended technique of application [28,39–42] and this has been cited as a possible reason for lack of efficacy of the vapocoolant spray in these studies [16,19,21,37].

Vapocoolant sprays last a short time, so the health care provider performing the needlestick procedure should have all the supplies readily available. This may be difficult in a busy ED. If the health care practitioner has to leave the patient and go and retrieve needed supplies, this allows the efficacy of the vapocoolant spray to wane. However, this should not be an issue, since the vapocoolant spray may be reapplied as often as needed.

The spray containers were identical (indistinguishable) and thus, blinded. The spray cans were masked and were stored together at the same (e.g. room temperature). Moreover, unmasking of the spray cans was not done until the study was over (e.g. enrollment ended and all data collection was completed). Although we sought to maintain blinding through obscuring aerosol containers, keeping the containers at the same temperature, and directing treatment sprays away from patients' and health care providers faces to avoid visual cues and olfactory detection, we cannot prove effective blinding.

There may be a difference in sensation on the skin between the vapocoolant spray and the placebo spray, which may lead to a bias. Patients could only be enrolled once in the study to avoid previous experience with this specific vapocoolant spray and because patients never had prior experience with a vapocoolant spray (or placebo spray) as a topical anesthetic in the past, he/she would be "naïve" and would not know what a vapocoolant spray (or placebo spray) would feel like, so it is unlikely that the patient responses would be biased. Since we did not want to influence the patient's response, we did not give them any pre-information about the sprays except that one was a placebo spray and one was the treatment spray.

We did collect details regarding the patients and the health care providers performing the procedures in order to document that the placebo and vapocoolant groups were similar at baseline and that the actual procedure of PIV cannulation was not significantly different between the two groups.

In summary, this prospective, double-blind, randomized controlled trial suggests that a topical vapocoolant spray (1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane) is not only effective in significantly relieving the pain of PIV cannulation in adults in the ED, but was also well tolerated with a majority of patients indicating they would use the vapocoolant spray in the future.

This vapocoolant spray appears to be safe with only a few minor adverse effects that resolved quickly (within 5–10 min), and had no lasting visible skin abnormalities. This is consistent with an animal study that found no microcirculatory effects (e.g., no significant changes in vessel diameter and inflammatory markers) [24].

6. Implications

The use of topical skin refrigerants or vapocoolants has numerous advantages: rapid onset, easy application, inexpensive, avoids needlestick injury, eliminates intradermal injection pain, increases procedural success rates, and improves patient satisfaction. Given the frequency of needlestick procedures in the health care setting, not just in the emergency department but throughout the hospital: on the inpatient floors and the operating room, in clinics and offices, and outpatient surgery centers: topical refrigerant sprays have wide applicability and likely, increased usage in the future.

Ethical issues

The study was approved by the Institutional Review Board (IRB).
Written informed consent was obtained from all subjects.
The study protocol was registered at ClinicalTrials.gov (NCT01670487).

Conflict of interest

Thus study was an investigator-initiated study supported by a research grant from the Gebauer Company. The sponsor had no involvement in the study other than funding and supplying the spray cans used for the administration of the placebo spray and the vapocoolant spray.

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