A PROSPECTIVE, BLINDED PLACEBO-CONTROLLED EVALUATION OF PAIN CONTROL USING A VAPOCOOLANT SPRAY DURING MINOR OFFICE PROCEDURES

Pain management has become an integral part of patient-centered care. This is due to physicians’ efforts to enhance the patient experience also because of Federal Joint Commission mandates.\(^1\),\(^2\)

Currently, pain relief includes newer pharmaceutical agents, longer-acting local anesthetics, pain pumps, regional anesthetic blocks, and/or combinations of the above. The concept of multimodal therapy for pain relief has grown in popularity.\(^3\)-\(^6\) However many regimens are costly and not supported by the evidence.\(^6\)-\(^7\)

Vapocoolant sprays (skin refrigerants) are topical anesthetics that can play a role because they have the benefits of rapid onset, non-drug formulation, and cost effectiveness.\(^8\)-\(^10\)

Skin refrigerants provide transient anesthesia via evaporation-induced skin cooling, which suppresses pain receptor sensitivity, resulting in decreased pain perception.\(^11\)

The purpose of this study was to assess the effectiveness of a blend of 1,1,1,3,3-Pentafluoropropane and 1,1,1,2-Tetrafluoroethane (Gebauer’s Pain Ease\(^\circ\), Gebauer Co. Cleveland, OH) in pain reduction associated with acrochordon (skin tag) removal in the office setting using a prospective, patient blinded placebo controlled model.

MATERIALS AND METHODS

A prospective, patient blinded, randomized, placebo-controlled efficacy study was conducted at our academic medical center in the outpatient office setting from January 2015 to August 2016.

The study protocol was approved by Institutional Board Review (IRB) and all patients gave verbal and written consent.

The study consisted of recruitment of 34 patients with 34 bilateral acrochordrons (68 in total).

Participants were healthy adults over 18 years of age who had at least one set of bilateral acrochordrons of comparable size in mirror image lesions. Only patients with the same dermatomal distribution were chosen to minimize pain variability due to anatomic location. That is, right and left sided lesions on the face, chest, or extremities. No lesions were continuous or same sided. Differences in pain were then assessed by comparing the lesion treated with the topical skin refrigerant to the opposite sided lesion, which was treated with a placebo water spray (Evian EauMinerale Naturelle, Evian-les-Bain, France). No local anesthetic preceded spraying. Subjects were excluded from the study if they demonstrated hypersensitivity to 1,1,1,3,3-Pentafluoropropane and 1,1,1,2-Tetrafluoroethane or were unable to accurately assess the 10-point numeric rating scale. The most commonly tested vapocoolant and mock spray locations included the neck: 14 (41.2%), and axilla: 13 (38.2%).

After prepping and cleansing the acrochordon excision sites with 70% isopropyl alcohol, each site was then sprayed with either the 1,1,1,3,3-Pentafluoropropane and 1,1,1,2-Tetrafluoroethane aerosol spray or placebo. The can containing mock water spray was refrigerated to below 10ºC, to approximate the temperature of the vapocoolant spray and assure the proper temperature control.

The application of the vapocoolant spray or placebo was completed by trained research fellows ensuring the administration of the product in the same consistent manner for all patients in both the vapocoolant and control groups.

Research fellows held each can at a distance of approximately three to seven inches from the excision site and sprayed onto the excision site for a duration of five seconds. Simple scissor excision was subsequently performed within a one-minute time window, as the vapocoolant anesthetic effect lasts for approximately 60 seconds. This corresponded...
with the manufacturer’s protocol in regard to time and distance.

Both spray cans were blinded to the subjects. Due to minor differences between two products, including variable transient skin whitening, jet force, and trajectory, research fellows performing the procedure could not be blinded. Immediately after each excision, patients were asked to score the pain level on a validated 10-point Likert scale with higher numbers indicating greater pain levels.

**STATISTICAL ANALYSIS**

Pain levels under control and experimental conditions for the 34 enrolled patients were recorded and summarized using means and 95 percent confidence intervals as well as medians and quartiles. The difference between vapocoolant spray and water placebo spray within each subject was calculated. Normality was assessed graphically and through the Shapiro-Wilk test. Both methods indicated departures from normality, so the primary analysis comparing pain by side was performed using the nonparametric Wilcoxon signed rank test. As a sensitivity analysis, a paired t-test was also performed.

Associations between the conditions and demographic factors were evaluated using Spearman correlations and Kruskal-Wallis or Wilcoxon rank sum tests. Analysis was performed using SAS software.

**RESULTS**

Of the 34 subjects enrolled in the study, 20 (58.8 percent) were female and 14 (41.2 percent) were male. The mean age was 60 years of age, ranging from 30 to 80 years. Twenty-nine (85 percent) patients were Caucasian, five (14.7 percent) included other ethnicities. Twenty-three (67.6 percent) patients reported less pain when the skin refrigerant was used for skin tag removal. Seven (20.6 percent) patients reported more pain. Four (11.7 percent) patients reported no difference in pain level between vapocoolant and the mock spray. No extremes in pain level were reported in any of the groups. Post-application, vapocoolant spray caused no apparent temporary or permanent soft tissue injury.

Both mean and median pain levels were lower in vapocoolant group (Group 1) patients compared to control group (Group 2). Wilcoxon ranked sum testing was used to compare median values and t-test was used to compare means. The mean pain level for vapocoolant group was 1.5 points (95% CI; -2.2, -0.7) lower than for the control group, p<0.001. Sensitivity analysis using a paired t-test showed similar findings (p<0.001). Table 1 summarizes patient pain levels between both groups.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Measure</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Pain Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Tag Pain</td>
<td>Median (P25,P75)</td>
<td>1.0 (0.0, 2.0)</td>
<td>2.0 (1.0, 4.0)</td>
<td>-1.0 (-2.0,0.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>1.5 (0.9,2.0)</td>
<td>2.9 (2.1,3.7)</td>
<td>-1.4 (-2.2,-0.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 summarizes associations with pain difference.

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>Statistics</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34</td>
<td>-0.01 [-0.35, 0.33]</td>
<td>0.96</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>-1.0 [-1.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>-2.0 [-3.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>5</td>
<td>-2.0 [-2.0, -0.5]</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>29</td>
<td>-1.0 [-2.0, 0.0]</td>
<td></td>
</tr>
<tr>
<td>Vapocoolant: Side</td>
<td></td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Left Side</td>
<td>15</td>
<td>-1.0 [-2.0, 1.0]</td>
<td></td>
</tr>
<tr>
<td>Right Side</td>
<td>19</td>
<td>-1.0 [-3.0, -0.5]</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Axilla</td>
<td>10</td>
<td>-1.00 [-2.0, -0.50]</td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>14</td>
<td>-1.5 [-3.0, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Other Location</td>
<td>10</td>
<td>-1.00 [-2.0, 0.00]</td>
<td></td>
</tr>
</tbody>
</table>

Statistics presented as Median [25th, 75th percentiles] with Wilcoxon rank sum test or Kruskal-Wallis test or Spearman’s correlation (95% CI).
None of the observed demographic factors including age, gender, ethnicity, side, or location of the vapocoolant spray were associated with pain differences in pain between sides though the study was not powered to evaluate this as a primary aim. (Table 2)

DISCUSSION:
Cryoanesthesia works by removing heat and lowering tissue temperature. It decreases the activation threshold of tissue nociceptors and the conduction velocity of pain nerve signals resulting in cold-induced neuropraxia. Much has been written about the use of vapocoolant sprays (skin refrigerants) for pain reduction in various medical settings. In plastic surgery and dermatology, topical anesthetic skin refrigerants have been used to reduce injection-site pain during botulinum toxin injections, filler treatments, subcutaneous injections, shave biopsies, curettage and incisional biopsies. Pain and accompanying anxiety varies significantly from patient to patient and can be substantial for some patients undergoing minor procedures. By treating mirror image lesions in similar anatomic locations, the patient essentially acted as his/her own control, thus minimizing pain variability.

The possibility of experiencing significant pain while undergoing office or outpatient procedures is real. Pain reduction during such procedures may significantly increase patient satisfaction.

The present study further confirms similar findings regarding pain reduction with the use of vapocoolants. Pretreatment using this topical anesthetic skin refrigerant (Gebauer’s Pain Ease) significantly reduced the discomfort associated with acrochordon removal in multiple anatomic locations and obviated the need for local anesthesia in this prospective blinded placebo controlled study.

The lack of sterility during these minor procedures does not appear to be a problem. Previous work has documented no increase in bacterial count on the skin of human volunteers following spray administration. In addition, no incidences of infection following a lesion removal occurred in this study or in our significant clinical experience.

As previously reported, there are important advantages to the use of vapocoolant over other anesthetic options such as EMLA cream and ice in an office setting. Vapocoolant spray has the benefit of rapid onset, when compared to EMLA cream which takes approximately 45 minutes to take effect. In addition, unlike EMLA, there is no patient clean up required. The cost of this multi-use spray, at an estimated rate of less than a dollar per application, is significantly less than EMLA or other topical anesthetics. Ice is an inexpensive and effective option, but requires refrigeration and can be messy with melting. Finally, adverse effects such as frostbite or skin discoloration from this procedure did not occur.

Pain can be difficult to accurately measure. Although the spray cans were similar in size and appearance, there was a slight difference in sensation and temperature between two sprays, which may have led to bias.

Finally, the efficacy of vapocoolant in other minor surgical procedures, such as nevus removal prior to injection of local anesthesia in various anatomical locations was not studied. It cannot be assumed that such a clinical scenario would be as effective.

Skin refrigerant is drug-free and maintains sterility, which combined with significantly decreased pain, rapid onset of action, and minimum office time required makes it an attractive option for improving patient experience during minor surgical excisions in the office setting.

CONCLUSION
This study provides new information regarding the efficacy of pain reduction with the use of vapocoolant spray using no additional local anesthetic measures during acrochordon removal in an outpatient setting. Its rapid onset, drug-free formulation, ease of administration, the need for no clean up, and low cost make this product a valuable tool for pain relief in the office setting.

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