Title: Evaluation of pain alleviating strategies during allergy shots (Subcutaneous immunotherapy): A randomized controlled study (Pain Perception with Allergy Shot Techniques: PPAST)

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Rationale and Purpose
Subcutaneous Immunotherapy (allergy injections) is a potentially disease-modifying therapy that is effective for the treatment of allergic rhinitis/conjunctivitis, allergic asthma and stinging insect hypersensitivity. Pain, which results from the irritation of nearby nerves is a common concern of patients, particularly in children, during or after the injections. This can be a stressful and negative experience for the children. There are various techniques available to minimize pain in general. However, there is a lack of published research on how to use these techniques in children receiving allergy injections. The purpose of this study is to evaluate and compare the efficacy of the standard of care method (Ethyl Chloride/Pain Ease Spray) and three non-pharmacological pain control devices (Buzzy Bee I, Buzzy Bee II and Shot Blocker) in decreasing the perception of pain during subcutaneous allergy injection in a pediatric allergy/immunology clinic setting.

Objective
• Evaluate and compare the effectiveness of utilizing various techniques to reduce the perception of pain during subcutaneous allergy injections in children

Possible Risks and Benefits
Risk Assessment
• The risks associated with study participation are consistent with standard of care risks. Potential risk for the study participants may be possible allergic reaction/skin irritation from the cold spray or ice pack or an increased level of anxiety.
Benefits Assessment

- The potential benefit associated with this research study includes a better understanding of study participant’s response to their assigned distraction technique. This study may help identify which technique is more beneficial to use in children receiving subcutaneous immunotherapy to decrease the perception of pain and reduce anxiety related to immunotherapy treatment.

Study Design and Duration

This is a randomized controlled study. Approximately 100 children, age 4 – 17 years, who are currently receiving subcutaneous immunotherapy, will randomly select a blinded envelope which assigns the distraction technique to be utilized during their study participation. There will be 25 envelopes assigned to each study group for a total of 100 envelopes. Each envelope will contain a paper with a colored sticker for the associated group assignment and number sequence.

The distribution of group assignment by number sequence and color is as follows:

- Intervenional Groups
  1. Shot Blocker® # 1-25 (RED)
  2. Buzzy I (vibrating only) # 26-50 (GREEN)
  3. Buzzy II (vibrating and ice wings) # 51-75 (BLUE)
- Control Group
  4. Ethyl Chloride/Pain Ease Spray # 76-100 (YELLOW)

The three interventional groups are currently marketed distraction devices. The control group is the current clinical standard of care option for pre-allergy injection application.

The study consists of two visits. Both visits will be conducted during the participants routine clinic visit for allergy injections. At the first visit the investigator will assess eligibility. An overview of the study requirements will be provided to parent/child and consent/assent will be obtained.

During the second visit, the child will be randomized to a distraction technique or standard of care group to be utilized with the allergy injection(s) administered at this visit. Adherence with institutional allergy injection guidelines will be maintained. Prior to the application of the distraction method, the investigator will interview the parent to collect data related to demographic information and their child’s current allergy health and treatment regime. The child’s pain perception will be assessed before and after the allergy injection. The parent’s perception of their child’s pain will be assessed after the allergy injection. The investigator will provide information on the application of the randomized method and will provide instruction on the completion of the pain scales and questionnaires. The investigator and study staff will not indicate a method preference or guide the child or parent with their pain level responses. After completion of the second visit, the child’s study participation is complete.

Inclusion & Exclusion Criteria

Inclusion Criteria
- Children aged 4-17 years on injection immunotherapy
- A minimum of three allergy injection injections prior to enrollment at Visit 1
• Child accompanied by parent or legal guardian

Exclusion Criteria

• Children with a known pain or sensory disorders
• Developmental delays lacking necessary cognitive ability
• Administration of any form of pain analgesic within eight hours of randomization at Visit 2

Study Procedures

Visit 1:
Children aged 4-17 years who present to receive their injection(s) in the allergy clinic will be screened by the Principal Investigator or Co-Investigator for study inclusion and exclusion criteria. During their routine post-allergy injection 30-minute wait time, the investigator and the research coordinator will provide the parent and child with an overview of the study design, the risk and benefits assessment and study requirements. The investigator will advise the parent/child of the pain analgesic administration exclusion for the randomization visit. After obtaining parental permission and child assent, the child will be considered enrolled in the study. A subject ID will be assigned. A visible mark placed on the child’s allergy injection chart will indicate the child is ready to be randomized at their next routine allergy injection visit.

Visit 2:
At a future allergy injection clinic visit the parent and the child will be asked if the child took any pain-relieving medicines, like Tylenol or Advil, within eight hours before coming to the clinic. If the participant needed this kind of medicine, the allergy shot appointment will be the same as before the study.

Study visit 2 will be completed at another routine allergy shot appointment. Preferably the next scheduled allergy injection visit.

If the participant did not take any pain relieving medicine within the previous eight hours, visit 2 will continue. The participants study group assignment will be determined. The envelopes identifying the four group assignments will be coded by number and color. The child will be presented with a basket containing all the envelopes. The investigator will instruct the child to select one envelope from the basket. The envelope selected at random by the child will determine the distraction method to be utilized prior to the allergy injection(s). The possible group assignments, one of three currently marketed distraction devices or the control group utilizing the current standard of care option, are listed below and are further detailed in Attachments I – III.

The four study groups are:

➢ Interventional Groups
   1. Shot Blocker®
   2. Buzzy I (with ice pack-wings)
   3. Buzzy II (without ice pack-wings)
➢ Control Group
   4. Ethyl Chloride/Pain Ease Spray
Before applying the assigned distraction method:
- Prior to randomization, the investigator will interview the parent to obtain the information needed to complete the Parent Demographic-Health-Treatment Questionnaire (Attachment V). The investigator will review the responses for any indicator of study ineligibility, ie, analgesic medication window.
- The investigator or study staff will review the Wong-Baker FACES Pain Rating Scale with the child. The child will be given a Wong-Baker FACES Pain Rating Scale form and asked to circle the face which most closely matches their current level of pain awareness prior to any intervention. (Attachment IV-a)
- The investigator or study staff will review the Numeric Pain Rating Scale (Attachment IV-b) with the parent. The parent will be instructed to circle the number on the scale which most closely matches their perception of their child’s pain level immediately after receiving the allergy injection.

Application of the distraction method and administration of the allergy injection:
- The investigator will apply the assigned distraction method per method specifications to the injection site area (subcutaneous region of the back of the upper arm).
- The investigator will administer the subcutaneous allergy injection(s) within the time frame specified for the assigned distraction device utilized or per the standard of care guidelines for the Pain Ease Spray, as appropriate. If the child’s treatment plan includes more than one injection, the assigned group technique will be utilized for all injections at the visit.

Post allergy injection procedures:
- Immediately following the allergy injection, the child will be provided with a second Wong-Baker FACES Pain Rating Scale form and be asked to circle the face which most closely matches their post-injection level of pain awareness.
- Immediately following the allergy injection, the parent will be reminded to circle the number on the Numeric Pain Rating Scale which most closely matches their perception of the child’s post-injection pain level.
- The participant and parent will then complete the routine 30 minute wait time for post allergy injections.

Study participation is complete at the end of Visit 2.

Prohibited Medications
Analgesic medications administered within eight hours of Visit 2 are prohibited.

Adverse Event (AE)
An AE is any unfavorable and unintended sign, symptom temporally associated with the use of the study technique and does not imply judgment about causality.

AE’s associated with the randomized intervention will be collected at Visit 2. The AE’s relationship to the distraction technique will be assessed using the following guidelines for causality and grading severity. AE’s related to the allergy injection will not be captured in this study.
**AE Relationship to Study Distraction Technique Guide**

<table>
<thead>
<tr>
<th>Relationship to Study Distraction Technique</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely</td>
<td>An event that follows a reasonable temporal sequence from administration of the study distraction technique; that follows a known or expected response pattern to the suspected study distraction technique; that is confirmed by stopping the use of the study distraction technique; and this is not explained by any other reasonable hypothesis.</td>
</tr>
<tr>
<td>Probably</td>
<td>An event that follows a reasonable temporal sequence from administration of the study distraction technique; that follows a known or expected response pattern to the suspected study technique; that is confirmed by stopping the use of the study distraction technique; and that is unlikely to be explained by the known characteristics of the subject’s clinical state or by other interventions.</td>
</tr>
<tr>
<td>Possibly</td>
<td>An event that follows a reasonable temporal sequence from administration of the study distraction technique; that follows a known or expected response pattern to that suspected study distraction technique.; but that could readily have been produced by a number of other factors.</td>
</tr>
<tr>
<td>Unrelated</td>
<td>An event that can be determined with certainty to have no relationship to the study distraction technique.</td>
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</table>

**AE Severity Grading**

<table>
<thead>
<tr>
<th>Severity (Toxicity Grade)</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Mild (1)</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>Moderate (2)</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate Instrumental activities of daily living (e.g., preparing meals, using the telephone, managing money)</td>
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<tr>
<td>Severe (3)</td>
<td>Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g., bathing, dressing, feeding self, using toilet, taking medications)</td>
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</table>

**Discontinuation and Replacement of study participants**
A child has the right to withdraw from study participation prior to the completion of Visit 2. Early withdrawal participants will be replaced one to one.

**Participant ID assignment**
The study participants will receive a Participant ID at Visit 1 which will be used for all data collection. The Participant ID used will range from 001 to 100. If a study participant withdraws before the completion of Visit 2, the Participant and associated group assignment will be replaced. Replacement Participant ID’s will be sequential beginning with the number 101.
**Data Collection**
Medication administration data collected will be limited to the participant’s current immunotherapy vial and dosing, distraction method utilized, site of the application method and, if applicable, antihistamine use and pain medication use. Demographic data collected will be age, race and gender. Symptom and health data point collection will target allergy injection reactions and the presence of allergic rhinitis, asthma and atopic dermatitis. (Refer to Attachment V). Pain perception data will be collected from both the child and parent using facial and numeric pain scales (Refer to Attachment IV). All data collected will be entered into an EXCEL data collection tool and stored on password protected, secure computers. The data will accessible only to the investigators and research coordinators in the study.

**Data Analysis**
Quantitative component data collected and evaluated for this study will include the number of patient participants within the allergy department, randomized interventions used, diagnoses including allergic rhinitis, asthma and atopic dermatitis, immunotherapy medication and dose, antihistamine and pain medication utilization, patient and parental pain scores, adverse reactions, age, race, and gender.
Quantitative component data collected for this study will be extracted into Microsoft Excel spreadsheets and analyzed using Excel functions. Target population demographic characteristics will be analyzed using descriptive statistics by the principal investigator with the level of significance set at $<0.05$.
All information collected as part of evaluating the impact of this study will be aggregated data from the project participants and will not include any potential patient identifiers. Participant confidentiality will be assured by coding the participants using individual identification numbers for any analysis activities occurring outside of the electronic health record. This information will be stored in accordance with Nemours IRB policies and procedures. The Excel files containing codified data without protected health information (PHI) will be stored in password protected files at Nemours, on a password protected desktop computer in a locked office space accessible only by the principal investigator and study designees. The risk to patients participating in this project will be no different from the risks of patients receiving standard care.

**Informed Consent Process**
- Children who meet study criteria will be identified by Principal Investigator or Co-Investigator in the allergy clinic.
- Parents/guardians and child will be given an overview of the study, participation requirements, and complete information on being a voluntary participant in a research study. They will be given an opportunity to read the consent form, have questions answered and decide if they want their child to participate.
- If both the parent and child are interested in participating in the study, one parent/legal guardian will be asked to sign a Parental Permission and Consent Form.
- Children between the ages of 7 and 17 who verbalize understanding and are agreeable to the Assent information and study expectations will be asked to sign a Child Assent or Adolescent Assent Form.
- The Principal Investigator, Co-Investigator or Research Coordinator obtaining consent will witness the parent and child signatures, will sign both documents and provide copies of the signed consent/assent to the parent and child.
**Participating Sites**
The study will be conducted at Nemours Children’s Specialty Care in the pediatric allergy clinics locations:
- Jacksonville Downtown
- Jacksonville South
- Fleming Island

**Literature Cited**


Psychological interventions for needle-related procedural pain and distress in children and adolescents: Cochrane Systematic Review - Intervention Version published: 04 October 2018


**Attachments:**
ShotBlocker™

ShotBlocker instantly reduces needle pain and anxiety associated with injections.

ShotBlocker distracts and comforts patients of all ages receiving intramuscular or subcutaneous injections to lessen the perceived pain and anxiety. ShotBlocker is an innovative, patented device that is both simple and easy-to-use.

Features and Benefits

- **Simple Design** – One ShotBlocker per patient is all you need.
- **Easy to Use** – Just press ShotBlocker firmly over the injection site and give the injection through or near the opening.
- **Immediate Effect** – The contact points on the underside create an immediate distracting effect. No waiting for topical anesthetics to take effect.
- **Versatility** – Useful in intramuscular injections, subcutaneous injections and other procedures that include a painful needle poke.
- **Cost Benefit** – Less costly than anesthetic creams or freezing sprays. (Faster, too.)
- **Smiles On Your Patient’s Faces** – Invented by a pediatrician to lessen the pain and anxiety experienced by his patients.
- **It Really Works!**

Product Offering

#8050 – Box of 50
#8100 – Box of 100

Bionix

Phone 1.800.551.6810  Fax 1.800.455.5678  Web www.BionixMed.com
How ShotBlocker® Works

ShotBlocker is a novel application of the gate control theory of pain management. ShotBlocker is a flexible plastic disk that has a number of blunt contact points on its underside. When pressed firmly against the patient’s skin at the injection site, ShotBlocker saturates the sensory signals distracting the patient from the pain signals caused by the needle poke.

How to Use

1. Select the injection site and prep the skin as usual.
2. Hold ShotBlocker so that the blunt contact points touch the patient’s skin at the injection site.
3. Press ShotBlocker FIRMLY against the skin. (A) DO NOT MOVE OR REMOVE SHOTBLOCKER UNTIL THE INJECTION HAS BEEN COMPLETED.
4. Immediately administer the injection in the usual manner through or near the central opening of ShotBlocker. For subcutaneous injections, angle the needle as needed to give the injection. (B) IF MORE THAN 20 SECONDS ELAPSE BETWEEN THE PLACEMENT OF SHOTBLOCKER AND THE INJECTION, COMPLETELY REMOVE SHOTBLOCKER FROM THE SKIN, REPEAT THE PROCESS BEGINNING WITH STEP 2.
5. After you have completed the injection and withdrawn the needle, remove and discard ShotBlocker.
II – Buzzy Bee I (with ice pack-wings) and Buzzy Bee II (without ice pack-wings)
ICE WINGS:
Wings will stay frozen 30 minutes at room temperature. For best pain relief, the Wings must be frozen solid to avoid shocking the skin. 

For best pain relief, place Wings toward the skin for more rapid freezing. If necessary, cool the cold side of the Wings before the skin.

Tips: 
- For effective relief, use at least 4 Wings simultaneously.
- Place Wings on the skin in a manner that will allow the Wings to reach as deep as possible into the skin. 

COMFORT STRAP: 
Our Comfort Strap is a flexible, adjustable design to prevent the Wings from being too tight or too loose. Simply pull the strap to relax the Wings or adjust the size of the Wings to fit the skin.

DIRCTIONS FOR USE: 
Immediately before use, remove the Wings from the freezer and attach them to the shirt, where they will stay frozen for an hour. To use, simply press the button on top of the Wings. The Wings will then release the frozen Wings and attach them to the shirt. 

Buzzy® has been shown to be effective in reducing pain during gastrointestinal procedures, including endoscopy, colonoscopy, and other gastrointestinal procedures.

INDICATIONS FOR USE:
- Pain relief during surgical procedures
- Pain relief during dental procedures
- Pain relief during medical procedures
- Pain relief during physical therapy

CONTRAINdications:
- Pregnancy
- Allergies to latex or neoprene
- History of sensitivity to cold

Warnings:
- For optimal effectiveness, Buzzy® should be worn for at least 30 minutes before the procedure.
- Buzzy® should be worn for at least 1 hour after the procedure.
- Buzzy® should not be worn on or near the eyes, ears, or nose.

CAUTIONS:
- For best results, Buzzy® should be worn on the skin in a manner that will allow the Wings to reach as deep as possible into the skin.
- Buzzy® should not be worn on or near the eyes, ears, or nose.

For additional information, please visit BuzzyHelps.com
III – Ethyl chloride spray

Rx only
Open the bottle while spraying.

INDICATIONS FOR USE:
Sabra's Ethyl Chloride is a superficial pain
reducer, used for topical applications to prepare
path associated with surgery, dentistry, wounds,
venipuncture, minor surgical procedures such as
biopsy, cysts, and lumps of small
instruments, and the temporary relief of minor sports
injuries. It is also intended for use as a transition tool
in the management of extraneous pain, restricted motion
and muscle tension.

PRECAUTIONS:
Do not apply to any areas of the body, including
areolar,union of the eyelid, or other sensitive
areas. Do not cause vomiting or general
anaesthesia, and may promote numbness.
Apply to the skin, and around the eyes in the
area where there is a significant amount of
swelling, or in the area where there is a
significant amount of tissue. The skin should
be treated with a gentle pressure upon
application to the skin, and around the eyes
in the area where there is a significant amount
of swelling, or in the area where there is a
significant amount of tissue.
IV – Data Collection Instruments for pain rating scales – (a) facial (b) numeric

**Wong-Baker FACES® Pain Rating Scale**

0 2 4 6 8 10
No Hurt Hurts Little Bit Hurts Little More Hurts Even More Hurts Whole Lot Hurts Worst

Used with permission.

**Instructions for Usage**

Explain to the person that each face represents a person who has no pain (hurt), some, or a lot of pain.

Face 0 doesn't hurt at all. Face 2 hurts just a little bit. Face 4 hurts a little bit more. Face 6 hurts even more. Face 8 hurts a whole lot. Face 10 hurts as much as you can imagine, although you don't have to be crying to have this worst pain.

Ask the person to choose the face that best depicts the pain they are experiencing.

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**Numeric Rating Scale**

**PAIN SCORE 0-10 NUMERICAL RATING**

0-10 Numerical Rating Scale

Instructions: Parent/ Guardian, please circle what pain level YOU perceive YOUR child to be in just after receiving their subcutaneous Immunotherapy (allergy shots).
**Demographic – Health – Treatment Questionnaire: Parent Interview**

*Investigator will interview the parent to complete this questionnaire. Questionnaire to be completed prior to administering allergy shot.*

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How old is your child?</td>
<td></td>
</tr>
<tr>
<td>2. What race/ethnicity is your child?</td>
<td></td>
</tr>
<tr>
<td>3. What gender is your child?</td>
<td></td>
</tr>
<tr>
<td>4. How long has your child been on allergy shots? (Estimate in weeks, months or years)</td>
<td></td>
</tr>
<tr>
<td>5. What is the number of allergy shots your child will receive today?</td>
<td></td>
</tr>
<tr>
<td>6. What color vial is your child on?</td>
<td></td>
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<tr>
<td>7. What is your child’s dose for the allergy shot?</td>
<td></td>
</tr>
<tr>
<td>8. What kind of allergy shot is your child receiving – venom / fire ant / environment?</td>
<td></td>
</tr>
<tr>
<td>9. Has your child ever had symptoms after receiving allergy shots?</td>
<td></td>
</tr>
<tr>
<td>If yes, explain:</td>
<td></td>
</tr>
<tr>
<td>10. Has your child taken any medication for pain today?</td>
<td></td>
</tr>
<tr>
<td>If yes: What was the name and dose of the pain medication?</td>
<td></td>
</tr>
<tr>
<td>For what reason was the medication given?</td>
<td></td>
</tr>
<tr>
<td>What time was the medication given?</td>
<td></td>
</tr>
<tr>
<td>11. Does your child use entheramine medications?</td>
<td></td>
</tr>
<tr>
<td>If yes: What was the name and dose of this medication?</td>
<td></td>
</tr>
<tr>
<td>How often is the medication given?</td>
<td></td>
</tr>
<tr>
<td>What time was the medication given?</td>
<td></td>
</tr>
<tr>
<td>11. Please check the ☐ if your child has any of the following symptoms:</td>
<td></td>
</tr>
<tr>
<td>☐ Allergic Rhinitis</td>
<td></td>
</tr>
<tr>
<td>☐ Asthma</td>
<td></td>
</tr>
<tr>
<td>☐ Atopic Dermatitis</td>
<td></td>
</tr>
</tbody>
</table>

**Participant ID:** ___________________________  **Visit:** ___/___/____

**Investigator Signature:** ___________________________  **Time form completed:** ___/___/____  **Date form completed:** ___/___/____