Rapid local anesthesia by lidocaine administered using STAR particles

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PROTOCOL TITLE: Rapid local anesthesia by lidocaine administered using STAR particles

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1.1	15SEP2021	Addition of additional information on the formulation of STAR particle gel and the safety of LET gel in combination with the STAR particle gel.
2.0	17NOV2022	Only 1 visit, only 15 participants, each get $100 for the visit, and phone f/u 1 day, 1 week, and 30 days after visit for skin changes. Also only 1 objective.
3.0	09DEC2022	Change in age of participants from 10-15 years old to 10-21 years old. The first 2 patients will be between the ages of 18-21 years old.
4.0	27APR2023	Addition of secondary objective to measure TEWL (transepidermal water loss) before and after application of STAR particles. Increase from 15 to 25 total participants.

Table of Contents

1. Study Summary

Project Title	Rapid local anesthesia by lidocaine administered using STAR particles
Project Design	Feasibility: First-in-humans clinical trial
Primary Objective	To determine if the combination of STAR particles with topical lidocaine formulations will expedite lidocaine delivery into skin and associated local anesthesia in comparison to a commonly used FDA-approved topical lidocaine (LET gel) in children.
Secondary Objective(s)	1. To evaluate 10% STAR-particle concentration and 500 μm length for lidocaine delivery into skin and associated local anesthesia in children. 2. To evaluate the TEWL on the skin before and after application of STAR particles
Research Intervention(s)/Interactions	STAR particles STAR particles are millimeter-scale particles with micron-scale projections made of biocompatible materials that painlessly disrupt the stratum corneum. As STAR particles are rubbed on skin, their microscopic projections create micron-scale pores in the stratum corneum to increase skin permeability to topical compounds independent of physicochemical properties. After the arms of the STAR particle puncture the skin, the elastic forces of the skin push the particles out.
Study Population	Children, adolescents and young adults (10 to 21 years of age)
Sample Size	25
Study Duration for individual participants	One visit with each visit lasting 2-4 hours and follow-up by phone 1 week and 4 weeks after the study visit.
Study Specific Abbreviations/ Definitions	VAPS – Visual analog pain scale; T_{SP} – Time to achieve anesthesia for STAR particles; T_{LET} – Time to achieve anesthesia for application of topical lidocaine (LET gel); ASRs – Acute skin reactions; PLGA – polylactic-co-glycolic acid; PLA – polylactic acid; GCMI – Global Center for Medical Innovation; TEWL - trans epidermal water loss
Funding Source (if any)	1998 Society (CHOA)
Study Site	Emory Childrens Center & Children's Healthcare of Atlanta

2. Objectives

A. Primary

1. To determine if the application of STAR particles (10% concentration and 500 μm length) applied prior to a topical lidocaine formulation (LET gel) will expedite lidocaine delivery into skin and associated local anesthesia in comparison to a commonly used FDA-approved application of topical lidocaine (LET gel) in children.

3. Background

Administration of more than 20 billion injections each year around the world, and placement of over 200 million intravenous catheters occurs annually in the United States. Pain caused by these and other procedures using hypodermic needles leads to fear of needles with negative consequences throughout the healthcare system. This fear often starts with children, of whom over 60% report a moderate to severe fear of needles. Other than their disease, hospitalized children claim that needles are their primary source of pain. There is evidence that many children acquire a fear of needles, which often continues and amplifies with age leading, for example, to refused blood sampling and vaccine administration in up to 40% of adults – all due to fear of needles.

Local anesthesia alleviates pain and fear associated with injections. The ideal local anesthetic for the clinical setting should be effective; have rapid onset; be fast and easy to load and administer with minimal user training; be portable; cause minimal pain; and be cost effective. Several methods of inducing local anesthesia exist, but each of them comes with limitations. Injectable lidocaine further increases fear and anxiety, and is painful. In contrast, topical anesthetics provide a painless and simple means of administering local anesthesia, but they unfortunately rely upon slow diffusion into the skin, leading to onset times of 20 to 60 minutes. This delayed onset is the main barrier for widespread clinical use of topical anesthetics for venous access procedures.

Lidocaine delivery into skin is blocked by the skin's stratum corneum barrier. To address this limitation, collaborators at Georgia Tech developed STAR particles, which are millimeter-scale particles with micron-scale projections made of biocompatible materials that painlessly disrupt the stratum corneum. These particles are made of titanium dioxide, a widely-used and safe ceramic material found in sunscreens, cosmetics, and paint. The STAR particles have no more risk for causing an adverse or serious adverse event than those of regularly used over-the-counter skin products. STAR particles are designed to incorporate invisibly into topical formulations applied to skin similarly to conventional topical skin products. The composition of the gel that will be used to formulate the STAR particles will be aloe gel. We are not aware of any risks posed by aloe gel, with the exception of the extreme rare cause of allergic or anaphylactic reaction. This aloe gel does not pose any obvious risks and is

contained in numerous products such as skin lotions and hair products. As STAR particles are rubbed on skin, their microscopic projections create micron-scale pores in the stratum corneum to increase skin permeability to topical compounds independent of physicochemical properties. STAR particles are designed small enough to be painless and hard to see, but large enough to enable delivery of molecules like lidocaine into skin. A STAR particle micro-projection length of a few hundred microns with a tapered geometry provides mechanical strength with a sharp tip (<10 μm radius) to facilitate insertion into skin without pain. The star-shaped geometry is designed to inhibit complete insertion of the particle into skin so STAR particles do not remain embedded in the skin. After the arms of the STAR particle puncture the skin, the elastic forces of the skin push the particles out. From our previous publication, the only adverse effect from the use of STAR particles was local erythema (Tadros AR et al. STAR particles for enhanced topical drug and vaccine delivery. Nature Medicine. 2020, 26: 341–347.).

The use of LET gel (Edge pharma, London) is indicated for topical anesthesia

in children for open wounds. We know from our previous study and publication that the STAR particles make miniscule punctures in the skin allowing a drug applied after can only enter the skin through these tiny pores that quickly seal. Using the STAR particles will be less invasive than any open wound a child could present with who would normally be receiving LET gel prior to suture closure or instrumentation of the wound. There would be no way that when LET gel delivered at the appropriate dose could ever enter the skin and overdose a patient than delivering it through any open wound that the LET gel is already approved for.

We realize that it is not uncommon for the FDA to test drugs or devices in adults (to assess safety and efficacy) prior to children, however, there would be no endpoint to determine if the STAR particles with LET gel is efficacious in adults, as few adults will be as interested or concerned with pain or local anesthesia.

4. Study Endpoints

A. Primary

1) Determine the T_{SP} of the STAR particle (10% concentration and 500 μm length) in children and compare to the T_{LET} and determine which application results in a more rapid time for local anesthesia.

B. Secondary

1) Determine the TEWL (trans epidermal water loss) measurement before and after application of the STAR particles and compare to the TEWL measurement before and after application of the aloe gel.

5. Study Intervention/Investigational Agent

This is a single-center study to compare the time to local anesthesia following application of STAR particles applied prior to skin application of topical lidocaine (LET gel) to application of topical lidocaine (LET gel) alone at one location in 25 healthy children, adolescents and young adults.

The investigational agent will be STAR particles made of titanium dioxide, a widely-used and safe ceramic material found in sunscreens, cosmetics, and paint. The particles will vary in concentration and length in order to find the optimal concentration and length. The star-shaped geometry is designed to inhibit complete insertion of the particle into skin so STAR particles do not remain embedded in the skin. After the arms of the STAR particle puncture the skin, the elastic forces of the skin push the particles out.

6. Procedures Involved

After signing the informed consent form, eligible participants will be enrolled in the study. At the visit, the TEWL will be measured using a wireless, portable Vapometer (Delfin Technologies, Finland) on the volar surface of the forearm where the the STAR particles will be applied. The STAR particle (in aloe gel) will be delivered to the skin immediately prior to the LET gel so that the time to achieve anesthesia for the topical lidocaine (LET gel) after STAR particle application (T_{SP}) can be compared to the time to achieve anesthesia for application of topical lidocaine (LET gel) alone (T_{LET}). The STAR particle will always be applied to the participant's right arm but the order of applying STAR particle will be randomized by a computer-generated random sequence. After application of the STAR particles, and prior to applying the LET gel, TEWL will again be measured using the wireless, portable Vapometer (Delfin Technologies, Finland).

The same procedure of measuring the TEWL will be followed on the forearm not receiving the STAR particle application (Aloe gel).

A. <u>LET Gel after STAR Particle Application (Right Arm):</u>

Topical lidocaine (0.5 grams of Lidocaine in LET gel) will be applied immediately after applying a STAR particle preparation to the volar surface of the mid-forearm at two locations (right antecubidal fossa and right wrist). Immediately after application of the STAR particles, the topical lidocaine (LET gel) will be applied. Immediately after the topical lidocaine (LET gel) is applied, pain will be assessed by the investigator every minute using the Pin-Prick Pain test. The time that the subject reports no pain (complete local anesthesia) will be recorded as the time to achieve anesthesia for the topical lidocaine after STAR particle application (T_{SP}) at both sites.

B. <u>LET GEL Application without STAR Particle Application (Left Arm):</u>

Topical lidocaine (0.5 grams of Lidocaine in LET gel) will be applied immediately after applying aloe gel (CONTROL) to the volar surface of the mid-forearm at two locations (right antecubidal fossa and right wrist). Immediately after application of the aloe gel, the topical lidocaine (LET gel) will be applied. Immediately after the topical lidocaine (LET gel) is applied, pain will be assessed by the investigator every minute using the Pin-Prick Pain test. The time that the subject reports no pain (complete local anesthesia) will be recorded as the time to achieve anesthesia for the topical lidocaine without STAR particle application (T_{LET}) at both sites.

The physician will also evaluate local tolerability by assessing the topical lidocaine (LET gel) alone and topical lidocaine (LET gel) post-STAR particle application site for acute skin reactions (ASRs), AEs, and SAEs on the day of application, 1 hour [±5 minutes] after the application, 24-hours after

application, one week after application, and 30 days after application. Specifically, the participant (and parent) will report if the participant's skin has erythema, edema, blistering, tenderness, bleeding, bruising, or any type of skin change. ASRs will be scored quantitatively with qualitative remarks as needed. ASRs, AEs, and SAEs of interest will be recorded.

7. Data Specimen Banking

This study will not be banking any specimens or data.

8. Sharing of Results with Participants

There are no expected incidental findings for the study. Results will not be returned to the participant.

9. Study Timelines

- Each subject will participate in the study for the one visit with phone follow-up one day to 30 days after the study visit.
- The duration anticipated enrolling all study participants is 2-3 months.
- The estimated date for the investigators to complete this study (complete primary analyses) is 12 months.

Study Procedures and Assessments

Procedures and Assessments	Study Visit	Follow-Up (24-hrs – 30 days)
Informed consent	X	
Medical history	X	
Inclusion and exclusion criteria	X	
STAR & Lidocaine application by clinician	X	
topical lidocaine (LET gel) application by clinician	X	
TEWL measurement before and after application	X	
Application site pain by VAS	X	
Application site pain by report	X	
ASRs, SAEs & AEs of interest	X	X

10. Inclusion and Exclusion Criteria

Inclusion criteria:

a. Children, adolescents and young adults, 10 - 21 years of age. The first 2 patients will be between the ages of 18-21 years old.
b. In good general health as determined by a medical history
c. Willing to provide informed assent with parental consent and follow study requirements

Exclusion criteria:

a. Is chronically using pain medication
b. Has a plan to move to another location in the next 12 months or foresees any other reason that participation in the study would be disrupted during the next 12 months
c. Has skin disorders or skin allergies
d. Has any previous allergy or adverse reaction to STAR particle ingredients (Titanium Dioxide)
e. Has abnormal (e.g., tattooed) skin at proposed the site(s) of STAR particle application
f. Has known neurological conditions that might affect sensory function or perception of pain
g. Has any condition (social or medical), which in the opinion of the investigator would make study participation unsafe, would interfere with adherence to the clinical study requirements, or would complicate data interpretation

11. Vulnerable Populations

The research does not contain vulnerable populations.

12. Local Number of Participants

25 children, adolescents and young adults 10-21-years of age.

13. Recruitment Methods

Participants will be recruited from Emory/CHOA pediatric Endocrine outpatient clinics. Participants will be recruited throughout the course of the study. Participants will be approached in clinic by the study PI or clinic provider about their interest in participating in this study. There will be no recruitment materials. Eligibility will be reviewed through questioning the participants, their parents, and review of the patients medical chart.

14. Withdrawal of Participants

The participant may be withdrawn from the research without their consent if they are not able to follow the protocol.

Given the minimal risk associated with STAR particles and previous history of STAR particles used in humans, there does not appear to be any obvious anticipated circumstances under which participants will be withdrawn from the research without their consent.

If participants withdraw from the research, data collected will be retained and utilized as an intention-to-treat (ITT) analysis.

15. Risk to Participants

The risks to this study are minimal. We will be applying STAR particles that should puncture the skin, allowing the lidocaine to have more rapid entry and then, due to the elastic forces of the skin, will push the particles out. From the time the STAR particles are applied to the skin, the possible risks would be expected to be local skin reactions at the site of STAR particle application including erythema, edema, tenderness, bleeding, and/or bruising.

A systemic reaction would be unlikely to occur, but due to the potential that the application and retention of STAR particles in the skin could facilitate bacterial entry into the skin, in addition to the local reactions listed above, systemic reactions including: fever, cough, nausea, vomiting, diarrhea, fatigue, and headaches could also occur. Based on previous human research with STAR particles, local and systemic reactions are unlikely to occur (1). Acute skin reactions (ASRs) will be scored quantitatively with qualitative remarks as needed. The application of the STAR particles is expected to have a minimal risk to the subject. It is possible subjects could describe the placement of the STAR particles as uncomfortable or painful, but based on previous human studies (1) this seems less likely. We will take precautions to prevent infections, such as using sterilized or low bioburden materials and wiping the skin with an alcohol swab before the study.

We hypothesize that the STAR particles will not remain in the skin. Our previous research on STAR particles suggests that the risk for application of STAR particles to be minimal (1). The only AE discovered in studying patients receiving a STAR particle application has been transient local erythema and otherwise, has been very well tolerated in healthy human participants. The article published in Nature Medicine can be referenced (Tadros AR et al. STAR particles for enhanced topical drug and vaccine delivery. Nature Medicine. 2020, 26: 341–347.) The composition of the gel that will be used to formulate the STAR particles will be aloe gel. We are not aware of any risks posed by aloe gel, with the exception of the extreme rare cause of allergic or anaphylactic reaction. This aloe gel does not pose any obvious risks and is contained in numerous products such as skin lotions and hair products.These particles are made of titanium dioxide, a widely-used and safe ceramic material found in sunscreens, cosmetics, and paint. STAR particles are designed to incorporate invisibly into topical formulations applied to skin similarly to conventional topical skin products.

The local anesthetic we are evaluating (LET gel) is approved in children for open wounds. We know from our previous study and publication that the STAR particles make miniscule punctures in the skin allowing a drug applied after can only enter the skin through these tiny pores that quickly seal. Using the STAR particles will be less invasive than any open wound a child could present with who would normally be receiving LET gel prior to suture closure or instrumentation of the wound. There would be no way that when LET gel delivered at the appropriate dose could ever enter the skin and overdose a patient than delivering it through any open wound that the LET gel is already approved for.

The LET gel delivered will be minimal, applied over a small surface area and below the limit of what would cause an adverse event even if that amount of LET gel was injected locally. The dose of the application will be 100-500 mg of LET gel to the skin which is far below toxic doses. The LET gel is FDA-approved for children 2-years and older and is used in individuals who need a local anesthetic and have an open wound. There have been no reports of adverse reactions or events associated with LET gel, however, an allergic reaction or even anaphylaxis, are always potential possibilities.

Based on previous clinical studies and FDA approvals of other drugs/devices using these materials, we therefore expect non-significant risk.

16. Potential Benefits to Participants

There is no direct benefit to the participant, however, there are potential future benefits to society from the understanding gained by the study.

17. Compensation to Participants

Study participants will receive $100 for completion of the study visit. Participants who drive to the visit will be reimbursed for parking in the designated ECC parking area.

18. Data Management and Confidentiality

Data will be stored either electronically in HIPAA compliant locations or in locked offices and cabinets. The data will be stored locally until we are allowed by the sponsor or Emory to destroy them. Only staff directly involved in completing study procedures will have access to the data. Staff listed on the delegation of authority log will be responsible for receipt and transmission of data. The coordinator or PI/Sub-I will be responsible for transporting the data locally.

If a participant declines to participate *or is ineligible to participate for any or* all portions of the study, the participant will not be assigned a study ID number and the study staff will refrain from collecting any data on the participant.

19. Provisions to Monitor the Data to Ensure the Safety of Participants

As this study is one with minimal risk, a DSMB will not be needed.

<u>Subject safety:</u>

- Specific subject safety parameters: subjects will report any safety-related issues or concerns to the PI (phone/email when not at a visit) or in person to the PI when at the visit.
- Subjects will report observations when at the clinic for the initial visit, and will record observations to be made available to the research team when either contacting the research team or the research team contacting them.
- The PIs will be responsible for safety monitoring

- If the subject has skin irritation, pain, itching, or infection, a topical medication could be applied to address the symptoms.
- The minimal risk associated with STAR particles makes it unlikely that a subject would develop any significant local or systemic consequence and therefore, other than subject choice or PI choice, there is not expected to be any condition that should stop the study.
- Deviations, AEs, and SAEs will be reported to the IRB by the PI.

Data Integrity:

- Specific data elements to be reviewed include: pain (if any) associated with STAR particle formulation insertion, local skin findings at initial placement, and local skin findings during the study.
- Monitoring of data will occur every month after every 5 subjects are enrolled so that data will be monitored 4-5 times during the study depending on how quickly enrollment is complete.
- The PIs will be responsible for data monitoring

Additional considerations for FDA regulated trials

- All study activities except production of the STAR particles will be done on-site
- The study team will self-monitor the study
- The study team will use Emory University's self-monitoring tool found on the CTAC website
- The first subject enrolled will trigger a self-monitoring event
- No Identification of deviations or failures that would be critical to study integrity

20. Provisions to Protect the Privacy Interest of Participants

Whenever possible, a study number, rather than the participants name will be used on study records. The participants name and other identifying information will not appear when study results are presented or published. All study documents will be kept in a locked office or secure server.

The sponsor representatives and regulatory authorities (e.g., IRB, OHRP) may inspect all documents and records required to be maintained by the investigator. The study team will permit access to such records.

Subjects will be made aware that all research activities are completely voluntary and will not impact the care they receive. They will also be informed that they are allowed to withdraw from the study at any time.

The quantitative data from this study will be uploaded to the DDL or another repository within 30 days of the primary manuscript publication. A description of the data repository will be included in the informed consent.

21. Economic Burden to Participants

There will be no costs for the participant associated with the research study.

22. Informed Consent

- Participants will be consented by the Principal Investigator in a private space in the CHOA Endocrine clinic or the ECC.
- There is no standard waiting period before the participant is approached for consent after being told about the study.
- The participant will be reminded throughout the study visit that participation is completely voluntary and that they are allowed to withdraw at any point during the visit or after the visit.
- The study will be explained thoroughly to the participant and the participant will be allowed to ask questions. The study team will give ample time to the potential participants to ask questions and decide whether they would like to participate. The participants will be reminded that the study is completely voluntary and that not participating will not affect their care for their medical condition. The staff performing the informed consent process will also ask the participant questions to verify understanding of the information relayed.

Non-English-Speaking Participants:

We will not enroll any non-english speaking participants since we are not able to get certified translations of the study questionnaire.

This study will need a partial HIPAA waiver for recruitment purposes ONLY (i.e. identifying potentially eligible subjects). As subjects are contacted, HIPAA authorization will be obtained.

23. Setting

The research will be conducted at the Emory Childrens Center (ECC) on the Emory University campus. All procedures will be performed by the study investigators when subjects are present for visits. Subjects will be in contact (email/phone) with the PI to report any unexpected issues relating to STAR particle placement or skin, if it occurs when not at the ECC for a visit.

All research procedures will be performed at the Emory Childrens Center on the Emory University campus.

24. Resources Available

We are performing this study as a feasibility study and believe we have enough resources (Emory/CHOA outpatient Endocrine clinic) to recruit the number of subjects we seek to study.

Eric I. Felner, MD, MS will devote 15% time to this study.

The PI (medical physician) and the research study team will be monitoring the subjects and subjects will be able to contact the study team for any potential consequences that could come about from the research.

The PI will review the protocol and procedures with the research study team.

25. Multi-Site Research When Emory is the Lead Site

N/A

26. References

1. Tadros, AR, Romanyuk A, Miller JC, Santiago A, Noel RK, O'Farrell L, Kwong GA, Prausnitz MR (2020). STAR particles for enhanced topical drug and vaccine delivery. Nature Medicine, 26: 341 – 347.