International Journal of Clinical Trials
Pulla SM et al. Int J Clin Trials. 2026 Feb;13(1):73-77
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: https://dx.doi.org/10.18203/2349-3259.ijct20260049

Protocol

Trial design and protocol of randomized controlled trial evaluating the efficacy of a non-invasive topical pain numbing device for prophylactic analgesia during routine vaccination in children

Swetha Madhuri Pulla, Jyothi Naik, Thirunavukkarasu Arun Babu*

Department of Paediatrics, All India Institute of Medical Sciences (AIIMS), Mangalagiri, Andhra Pradesh, India

Received: 11 October 2025
Accepted: 17 January 2026

***Correspondence:**
Dr. Thirunavukkarasu Arun Babu,
E-mail: babuarun@yahoo.com

ABSTRACT

Background: Pain associated with vaccination is a common cause of anxiety among children and their parents. While pharmacological and non-pharmacological interventions have been explored to reduce pain, their use is not widespread in practice. Cryoanalgesia using a non-invasive pain numbing device is a novel approach that has shown promise during minor procedures.
Methods: This is a prospective, double-blinded, randomized controlled trial evaluating the efficacy and safety of a non-invasive topical pain numbing device in reducing pain during routine childhood vaccination. Children aged 6 weeks to 10 years presenting to the pediatric OPD for immunization will be recruited. Participants will be randomly allocated to either the intervention (device) or control (sham device) group using block randomization. Pain will be assessed using the FLACC scale at 0, 5 and 15 minutes post-vaccination.
Conclusions: If the device proves effective in reducing vaccination-associated pain, it could be implemented widely to improve vaccine compliance and reduce vaccine hesitancy.
Trial Registration: Clinical trials registration number is CTRI/2025/03/083734.

Keywords: Vaccination, Children, FLACC score, Pain relief, Randomized trial

INTRODUCTION

Vaccination remains the most effective public health strategy to reduce childhood morbidity and mortality from infectious diseases. Despite significant advances, pain associated with injections is a major source of distress, often overlooked in clinical practice. Immunization is estimated to save approximately 2–3 million lives each year worldwide, decreasing the infant mortality rate from 65 per 1000 live births in 1990 to 29 per 1000 live births in 2018.[1]

Injection-related pain during vaccination contributes to anxiety in children and parents. Despite the availability of evidence-based pharmacological and non-pharmacological pain-reducing strategies, they are infrequently practiced. Needle pain can lead to negative attitudes towards vaccination, hesitancy, and noncompliance. The WHO defines vaccine hesitancy as a delay in acceptance or refusal of vaccines despite availability of vaccination services.[2,3]

Oral analgesics, breastfeeding, sucrose or glucose solutions, and distraction techniques have been employed with varying success.[3-5] Emerging evidence shows that using automatic devices for procedures like heel pricks results in consistently lower pain scores compared to manual methods, underscoring the role of technology in procedural pain reduction.[6]

A portable non-invasive pain numbing device works on the principle of cryoanalgesia, freezing and numbing the

application area within 8–10 seconds. It is a novel, non-invasive method and offers a simple, rapid, and side-effect-free technique to reduce procedural pain. Several studies demonstrate its safety and efficacy, but evidence regarding its role during routine childhood immunization is limited.[7]

This study aims to evaluate whether a non-invasive topical cryoanalgesic device can effectively reduce pain perception during childhood vaccination.

Objectives

Primary objective

Primary objective of the study is to determine the efficacy of a non-invasive topical pain numbing device for prophylactic analgesia during routine childhood vaccination.

Secondary objective

Secondary objective of the study is to assess the tolerance and adverse effects of the device during routine childhood vaccination.

Novelty

To the best of our knowledge, this is the first study evaluating the use of a non-invasive pain numbing device for prophylactic analgesia during routine childhood immunization.

METHODS

Trial design

This study was a prospective, double-blinded, randomized, placebo-controlled trial.

Study setting

This study was presented at Department of Pediatrics, AIIMS Mangalagiri, Andhra Pradesh, India.

Eligibility criteria

Inclusion criteria

Children aged 6 weeks to 10 years attending the outpatient department of Pediatrics for immunization will be included. Written informed consent will be obtained from parents or legal guardian of all participants before enrollment.

Exclusion criteria

Children with chronic illnesses, coagulation disorders, neurological diseases, known allergies, or on analgesic medications from last 24 hrs will be excluded.

Sample size

Based on previous studies, assuming a mean FLACC score of 7.5 (SD=2) in the control group and expecting a 10% reduction in the intervention group, with 80% power and 5% significance, the required sample size is 84 (42 per group), rounded off to 100 (50 in each group).

Ethical considerations

The study was approved by the Institutional Ethics Committee (IEC approval number: AIIMS/MG/IEC/2024-25/221) and registered under the Clinical Trials Registry of India (CTRI/2025/03/083734). Participant confidentiality will be maintained, and informed consent and oral assent (for 7-10 years) will be obtained.

Randomization

Block randomization with block sizes of six will be used to generate the allocation sequence with the ratio of 1:1 will be done through computer automatic randomization table generation. Sequence generation will be done through randomization software. (SNOSE) sequentially numbered opaque sealed envelope technique will be used for allocation concealment.

Allocation concealment mechanism

The list generated using the software will be kept in opaque, sealed envelope. Sealed envelopes containing the group allocation coded as A and B will be made for randomly allocating participants. Children will be assigned to two groups according to allocation and one group will receive analgesia by cryoanalgesic device (study group) and a sham device will be used for the other group (control group). The physical characteristics of devices used in both groups will be matched for maintaining blinding.

Blinding

The participating children, their parents and the health care professionals involved in study will not know the group allocation and device administered to the participant. Intervention (device application) will be done by one person, outcome assessed by other person (primary investigator). Concealment will be disclosed only after statistical analysis is performed and results are locked.

Study procedure and implementation

After consent, envelopes will be opened sequentially and group allocation to any one of two groups will be done as per coding inside envelope. Every enrolled child will receive intervention(device) either participants will be allocated to either Group A (device) or Group B (sham device). The intervention will be applied before vaccination. Pain scores will be assessed using the FLACC scale at 0, 5 and 15 minutes post-vaccination.

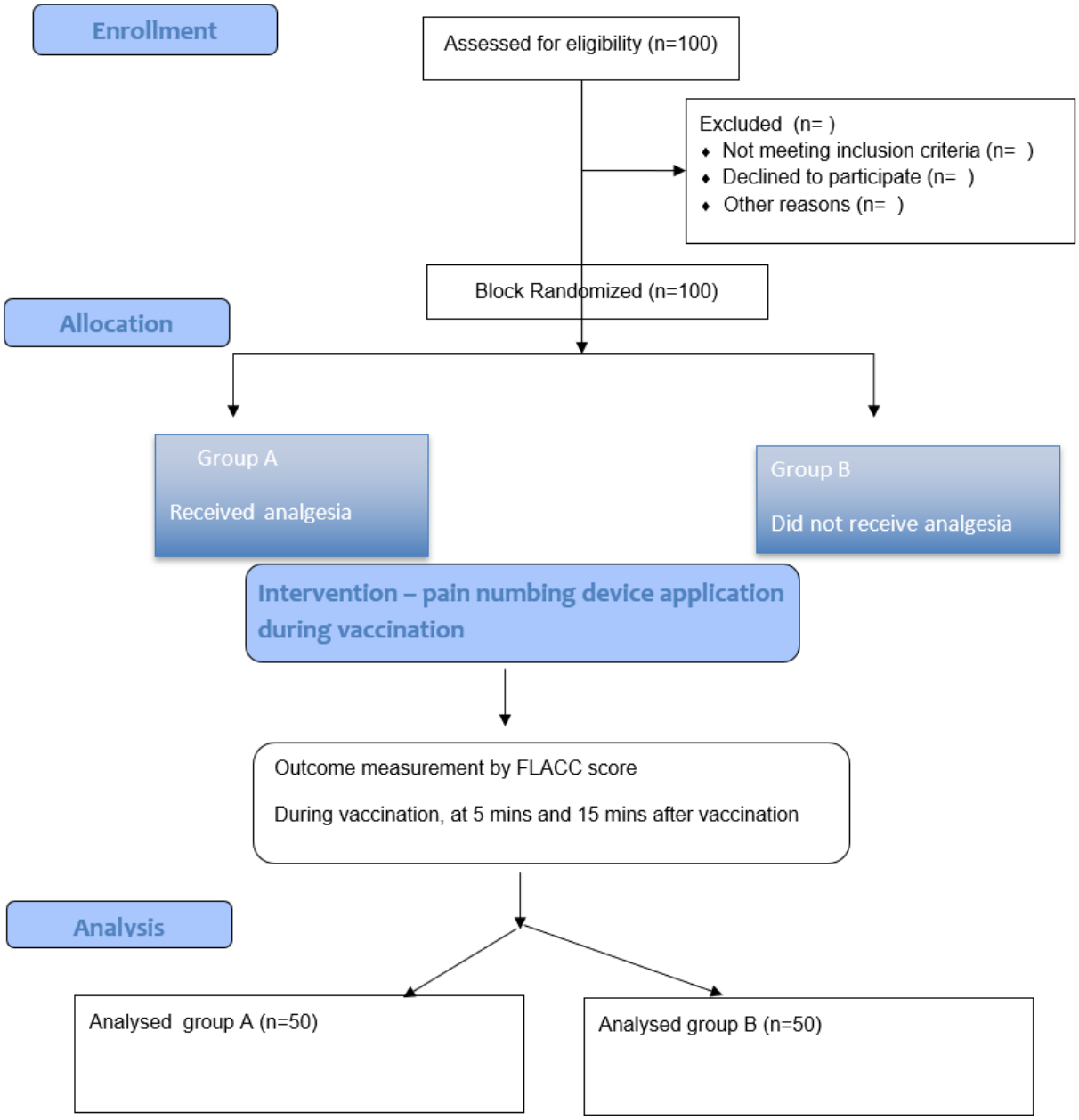

Figure 1: Flow diagram.

Intervention

Group A will receive cryoanalgesia through a non-invasive topical numbing device. Group B will receive a sham device application with no numbing effect. Devices will have similar physical appearance.

Instrument

The cryoanalgesic device used in this study is EXOCOOL, manufactured by Camex Wellness Ltd, Gujarat, India. It is a portable, compact unit with a medical-grade aluminium alloy tip, designed to ensure safe application across all skin types. The device measures 3.6×4.4×16 cm, weighs approximately 120gm and operates without need for batteries. For optimal performance the device is prefrozen to a temperature below 12 C, internal sensors with light signals guide optimal use: Red- needs more freezing, Green- ready, Blue- liquid cold. It is reusable up to 1500 times, proper hygiene is ensured by sanitizing the tip before and after use. It is suitable for all age groups and no side effects reported.

Study tool

The FLACC scale assesses face, legs, activity, cry, and consolability, each of these parameters are ranked on three-point scale (0-2) as per response severity as described for a total score between 0 and 10 (8). It is easy

to administer this scale and is validated for post-procedural pain measurement in children from 2 months to 7 years of age. It is a reliable and valid scale used in many studies involving children.

Outcome measures

Primary outcome: To study efficacy of pain numbing device during routine childhood immunization by assessing FLACC score done at 0, 5, 15 mins after vaccination.

Secondary outcome: To study safety, tolerability of pain numbing device during routine childhood immunization.

Statistical analysis

Intention to treat analysis will be performed. Continuous variables like age, FLACC score will be summarized as mean with standard deviation/ mean with interquartile range. Categorical variables like gender, study group will be summarized as frequency/proportion. The comparison of FLACC score between the groups at each time point will be done using independent students T-test/Man Whitney U test. Change in FLACCS score over a period of time between the groups will be assessed using 2way repeated measures ANOVA. Post HOC analysis will be done as appropriate.

DISCUSSION

Vaccination continues to be the most effective public health measure to reduce childhood morbidity and mortality from infectious diseases. However, pain caused by injections is often overlooked in clinical settings, despite being a significant cause of distress among children. Although a variety of evidence – based pharmacological and non-pharmacological approaches are available to reduce vaccination-related pain, they are rarely incorporated into routine practice, even if explored, they offer inconsistent relief.[9] Effective pain management during pediatric procedures is crucial not only to reduce physical discomfort but also to minimize long-term psychological distress, which may influence future health care interactions.[10,11] Some studies have investigated non-invasive cooling methods to reduce pain during procedures like intravenous cannulation, and these have shown to be simple, effective and more beneficial than traditional techniques.

Non-invasive pain numbing devices, which work by freezing and numbing the skin within 8-10 seconds, are easy to use and found to be effective and safe for use in children. Many such devices are already available commercially and are considered safe with no reported adverse effects. However, there is limited evidence supporting their use specifically during routine immunizations.

This study evaluates a potentially effective, low-cost, non-pharmacological intervention to alleviate vaccination pain. If proven effective, this device can be integrated into routine immunization settings to enhance the experience of children and their caregivers, ultimately improving vaccination uptake.

Strengths

Strengths of this study include its robust design as a randomized controlled trial with double blinding which minimises bias and enhances reliability of results. The use of a validated pain assessment tool, the FLACC score further strengthens the credibility of findings. Additionally, this study holds novelty as it is the first study to evaluate the use of non-invasive cryoanalgesic device for pain relief during routine childhood immunization

Limitations

There is an inherent subject bias, in form variation in pain expression among children which is difficult to control. Furthermore, as study is being conducted at a single centre, results may not be generalizable to all. Another potential limitation in pediatric pain-related research is the difficulty in obtaining parental consent due to concerns regarding safety, discomfort, and lack of immediate benefits, as observed in prior pediatric trials.[10]

CONCLUSION

This RCT will assess the role of cryoanalgesia in reducing vaccination-related pain in children. The study aims to provide evidence for the need for prophylactic analgesia during routine vaccination in children. If this study demonstrates a significant reduction in vaccination-associated pain, it could have a considerable impact on the National Immunization Program. This intervention has the potential to not only increase vaccine acceptance among both parents and children but also alleviate their anxiety and fear of needle pricks. Additionally, it may help reduce vaccine hesitancy and improve overall vaccine coverage.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee and trial has been registered at central trial registry of India, CTRI

REFERENCES

1. Nandi A, Shet A. Why vaccines matter: understanding the broader health, economic, and child development benefits of routine vaccination. Hum Vaccines Immunother. 2020;16(8):1900–4.
2. Taddio A, McMurtry CM, Logeman C, Gudzak V, de Boer A, Constantin K, et al. Prevalence of pain and fear as barriers to vaccination in children -

Systematic review and meta-analysis. Vaccine. 2022;40(52):7526–37.
3. Shah V, Taddio A, McMurtry CM, Halperin SA, Noel M, Pillai Riddell R, et al. Pharmacological and Combined Interventions to Reduce Vaccine Injection Pain in Children and Adults: Systematic Review and Meta-Analysis. Clin J Pain. 2015;31(10 Suppl):S38-63.
4. Pasi R, Babu TA, Kallidoss VK. Efficacy of oral mefenamic acid versus paracetamol as a prophylactic analgesic for needle pain in children receiving vaccination: a three-arm, parallel, triple-blind, placebo-controlled MAP VaC randomized controlled trial. Ther Adv Vaccines Immunother. 2023;11:25151355231216122.
5. Taddio A, Appleton M, Bortolussi R, Chambers C, Dubey V, Halperin S, et al. Reducing the pain of childhood vaccination: an evidence-based clinical practice guideline (summary). CMAJ Can Med Assoc J J Assoc Medicale Can. 2010;182(18):1989–95.
6. Venkatachari M, Babu TA. Variables Impacting Pain Perception With Various Heel Prick Devices in Neonates. Indian Pediatr. 2023;60(11):963.
7. Xess PA, Sarna R, Sethi S, Chauhan R, Meena SC, Saini V, et al. Effect of CoolSense and EMLA Cream on Pain During Intravenous Cannulation in Pediatric Population: A Randomized, Controlled Trial. Indian J Pediatr. 2024;91(2):119–24.
8. Kochman A, Howell J, Sheridan M, Kou M, Shelton Ryan EE, Lee S, et al. Reliability of the Faces, Legs, Activity, Cry, and Consolability Scale in Assessing Acute Pain in the Pediatric Emergency Department. Pediatr Emerg Care. 2017;33(1):14–7.
9. Doyle L, Colletti JE. Pediatric procedural sedation and analgesia. Pediatr Clin North Am. 2006;53(2):279–92.
10. Pasi R, Babu TA. Reasons for parental refusal to provide consent in a pediatric randomized controlled trial: Lessons learned. Pediatr Companion. 2023;2(2):41–3.
11. Babu TA. Procedural Sedation in Children—What is Recommended? Indian Pediatr. 2013;50(5):517.

Cite this article as: Pulla SM, Naik J, Babu TA. Trial design and protocol of randomized controlled trial evaluating the efficacy of a non-invasive topical pain numbing device for prophylactic analgesia during routine vaccination in children. Int J Clin Trials 2026;13(1):73-7.