

Official Title: Efficacy of a Vapocoolant Spray in Reducing Pain During Capillary Glucose Testing: A Randomized Crossover Trial

1.1. Study Design and Settings

This study was a single-center, randomized, controlled crossover trial with a 1:1 allocation ratio, conducted in the Emergency Department of Bolu Abant Izzet Baysal University Training and Research Hospital. University Clinical Research Ethics Committee approved the study protocol (protocol number: 2024/384), and the trial adhered to the Declaration of Helsinki.

In reporting the study, the Consolidated Standards of Reporting Trials (CONSORT) guidelines [10] were followed, and the study was registered at ClinicalTrials.gov under the identifier NCT06789055.

1.2. Participants

Eligible participants were patients aged 18 years or older scheduled for at least two capillary blood glucose measurements for any clinical indication during their ED visit, and those who provided informed consent to participate in the study. Exclusion criteria were: (1) known allergy to vapocoolant spray components, (2) conditions affecting pain sensation (e.g., peripheral neuropathy, peripheral arterial disease), (3) cognitive impairments precluding VAS use (e.g., dementia, Alzheimer's disease), and (4) severe concurrent conditions that could confound pain evaluation (e.g., acute trauma or administration of analgesics in the ED). Participants were enrolled consecutively from the emergency department patient population during routine clinical care. Enrollment began on March 10, 2025, and was completed on March 14, 2025, upon reaching the target sample size.

1.3. Groups and Interventions

Participants underwent a standardized protocol for capillary blood glucose testing [11] and received both interventions (vapocoolant spray and placebo) in a randomized sequence in two different blood glucose measurements. Patients were randomly allocated into two groups:

- **Group 1:** For the first capillary blood glucose measurement, a placebo (sterile water) was sprayed onto the designated measurement site prior to the glucose testing procedure. For the second measurement, a vapocoolant spray was applied to the corresponding site on the contralateral hand before the glucose testing procedure.
- **Group 2:** For the first capillary blood glucose measurement, a vapocoolant spray was applied to the designated measurement site prior to the glucose testing procedure. For the second measurement, a placebo (sterile water) was sprayed onto the corresponding site on the contralateral hand before the glucose testing procedure (Fig. 1).

The crossover design allowed each participant to serve as their own control and minimized potential acclimatization effects associated with repeated capillary glucose testing. To address the possibility that the second measurement might be better tolerated due to reduced anticipatory anxiety and increased familiarity, the sequence of interventions was randomized to distribute this order effect equally between study conditions [12, 13]. Procedural comparability was maintained by performing the second measurement on the contralateral hand's corresponding finger according to the assigned sequence; for example, if the right index finger was used first, the left index finger was used for the second measurement. Finger selection for the initial glucose measurement was not otherwise restricted, and no additional punctures beyond those clinically indicated were performed. Given the highly localized and brief duration of action of ethyl chloride spray, any residual treatment effect between measurements was considered negligible.

Intervention Procedures

1) Spray applications

Patients underwent spray application to the designated measurement site prior to capillary blood glucose measurement, according to their assigned groups.

Vapocoolant spray application:

A vapocoolant spray containing ethyl chloride (Shutz Plus Clorethyl Cooling Spray) was applied to the fingertip from a distance of 30 cm for 10 seconds to provide short-term cutaneous analgesia through rapid evaporative cooling.

Placebo application:

A sterile water spray, identical in appearance to the vapocoolant spray, was applied to the fingertip from a distance of 30 cm for 10 seconds.

2) Glucose measurements

Following the spray application (either a vapocoolant spray or a placebo), the area was cleansed with an alcohol swab in a circular motion for 10 seconds. The fingertip was then punctured with a standard lancet (Ayset 30-gauge). The first drop of blood was wiped away, and the subsequent drop was used to measure glucose with the STANDARDTM GlucoNavii GDH device [11].

1.4. Data Collection

Demographic data (age, sex, comorbidities), diabetes medication use, glucose levels, and Visual Analog Scale (VAS) scores were recorded on standardized forms. Measurements were taken during routine clinical care, minimizing the need for additional punctures beyond those medically necessary.

Outcome Measurement

The primary outcome of this study was pain perception during capillary blood glucose measurement, assessed using the VAS. The VAS consists of a 100-mm line, with endpoints labeled "no pain" (0) and "worst pain imaginable" (100). Participants were asked to mark their pain level immediately after each measurement. The pain score was determined by measuring the distance (in mm) from the "no pain" end to the participant's mark on the scale.[14] Secondary outcomes included adverse events (e.g., pruritus, coolness and numbness, erythema, burning sensation) [15].

1.5. Sample Size Calculation

The sample size was calculated using G*Power 3.1 software, with a Type I error rate (α) of 0.05 and statistical power ($1-\beta$) of 0.80 [16]. Assuming a moderate effect size (Cohen's $d = 0.5$) for the difference in pain scores between vapocoolant spray and placebo, corresponding to a clinically meaningful reduction of approximately 10 mm on the VAS, a total of 77 participants was determined to be sufficient [17, 18]. In this crossover design, each participant contributed two measurements (one with a vapocoolant spray and one with a placebo), resulting in 77 measurements per intervention [19].

1.6. Randomization and Masking

The random allocation sequence was generated by an investigator not involved in direct patient care. Participants were randomized into two sequence groups using an online randomization tool with block randomization. A fixed block size of four was used to ensure balanced allocation between groups. Following randomization, group assignments were placed in sequentially numbered, opaque, sealed envelopes.

- Group 1 received a placebo during the first measurement and a vapocoolant spray during the second measurement.

- Group 2 received a vapocoolant spray first, followed by a placebo during the second measurement.

To ensure blinding, both the vapocoolant spray and placebo containers were wrapped in opaque white paper to conceal their contents and labeled only as “1” or “2” according to the assigned sequence. Apart from these numerical labels, the containers were identical in appearance. This labeling procedure was performed by an individual who was not involved in patient care, outcome assessment, or data analysis. Thus, both participants and the care providers administering the spray remained blinded to the intervention type.

2. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0. The distribution of continuous variables was assessed visually using histograms. Categorical variables were presented as frequencies with percentages. Normally distributed variables were presented as mean and standard deviation, while non-normally distributed variables were presented as medians with interquartile ranges (IQRs).

The primary outcome was the within-patient difference in pain scores between vapocoolant spray and placebo applications, measured using the VAS. Because the study used a crossover design and pain scores were paired within the same participant, the primary comparison was performed using the Wilcoxon signed-rank test. The paired difference was defined as placebo VAS minus vapocoolant VAS, and the point estimate with its 95% confidence interval was calculated using the Hodges-Lehmann method. Multiple-group comparisons were performed using the Kruskal-Wallis test.

Missing data for the primary outcome were handled using a complete-case approach. Participants who did not complete both capillary blood glucose measurements (n=3) were

excluded from the paired primary outcome analysis but were retained in the descriptive baseline summary. All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant.