Evaluation of Three Non-invasive Analgesic Techniques in Pain Prevention During Injections

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Background

The application of injectable substances, whether local anesthetics, vaccines, drugs or cosmetics, can cause significative pain and discomfort. There exists a wide range of variables that may influence the subjective experience of each patient during the performance of an injection, like the type of substance utilized, the volume of liquid infiltered, the anatomic location, or whether a non-invasive anesthetic technique is utilized (1).

As regards traditionally used non-invasive analgesic techniques for pain control during injections, there are a limited amount of clinical trials that provide an adequate level of evidence in this field (1). Some studies claim to have proven the efficacy of cold, anesthetic creams or vibration for pain control during injections (2). Notwithstanding, these studies have generally focused in comparing only the studied analgesic technique with a control group, instead of comparing anesthetic techniques among themselves (2). Furthermore, it is even scarcer the amount of studies focused in the field of cosmetic subcutaneous injections; whereas most of the reported studies have been performed in the context of anesthetic injection in odontology, intravitreal injections, or blood sample collection in pediatric population (3).

The use of cold for pain control during injection has been traditionally utilized in different contexts. Notwithstanding, scientific evidence in favor of the use of cold as an analgesic agent in the context of injections is scarce, and has a low level of evidence (4). The mechanisms through which cold is considered to elevate pain threshold are: an alteration of nerve conduction, reduction of muscle spasms and prevention of tissue edema (4-6).

The application of topical anesthetic cream is frequently used for minimizing pain caused by injections (3). The main disadvantage of this method is the time required for the anesthetic effect to start. Different studies have shown that penetration depth of the anesthetic effect is of 3mm after 30-60 minutes, and 5mm after 90-120 minutes (7,8). Many authors reported better results in pain control with the use of this type of substances than with placebo (9-13). Notwithstanding, most of those studies were focused in the use of topical anesthetics in oral mucosa prior to anesthetic injection in odontology procedures, and most of them included reduced samples (lower than 50 subjects) (9,10,14-18). There is also a relevant amount of studies that did not find any statistically significant differences in terms of pain control between control and intervention groups (14-19).

Vibration analgesia was first described in 1984 by Reed et al (20). It is the non-invasive method that has been studied less in classic literature, although in the last 10 years its interest has grown significantly, with the apparition of new studies in different clinical contexts, and with results that generally favor its use (21-25). The studies that have reported an improvement in pain control have been performed in the field of ondontology (21), infiltration of local anesthetics in children (22), keloid infiltration (23), botulinum toxin injection (24), and hyaluronic acid injection for lip filling (25). Notwithstanding, other studies have reported unfavorable results for this analgesic method, in the field of venipuncture in children, and anesthetic injections in odontology (26-28). All authors agree that the amount of studies focused in this type of anesthetic method is scarce, and that more studies with a higher level of evidence are required in order to evaluate its real utility (20-31).

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Objective

In this clinical trial, we evaluated the effectivity of three non-invasive analgesic techniques (cold, anesthetic cream and vibration), including a control zone, in 100 healthy individuals, by performing subcutaneous forehead injections of 0,1ml physiologic saline.

Hypotheses

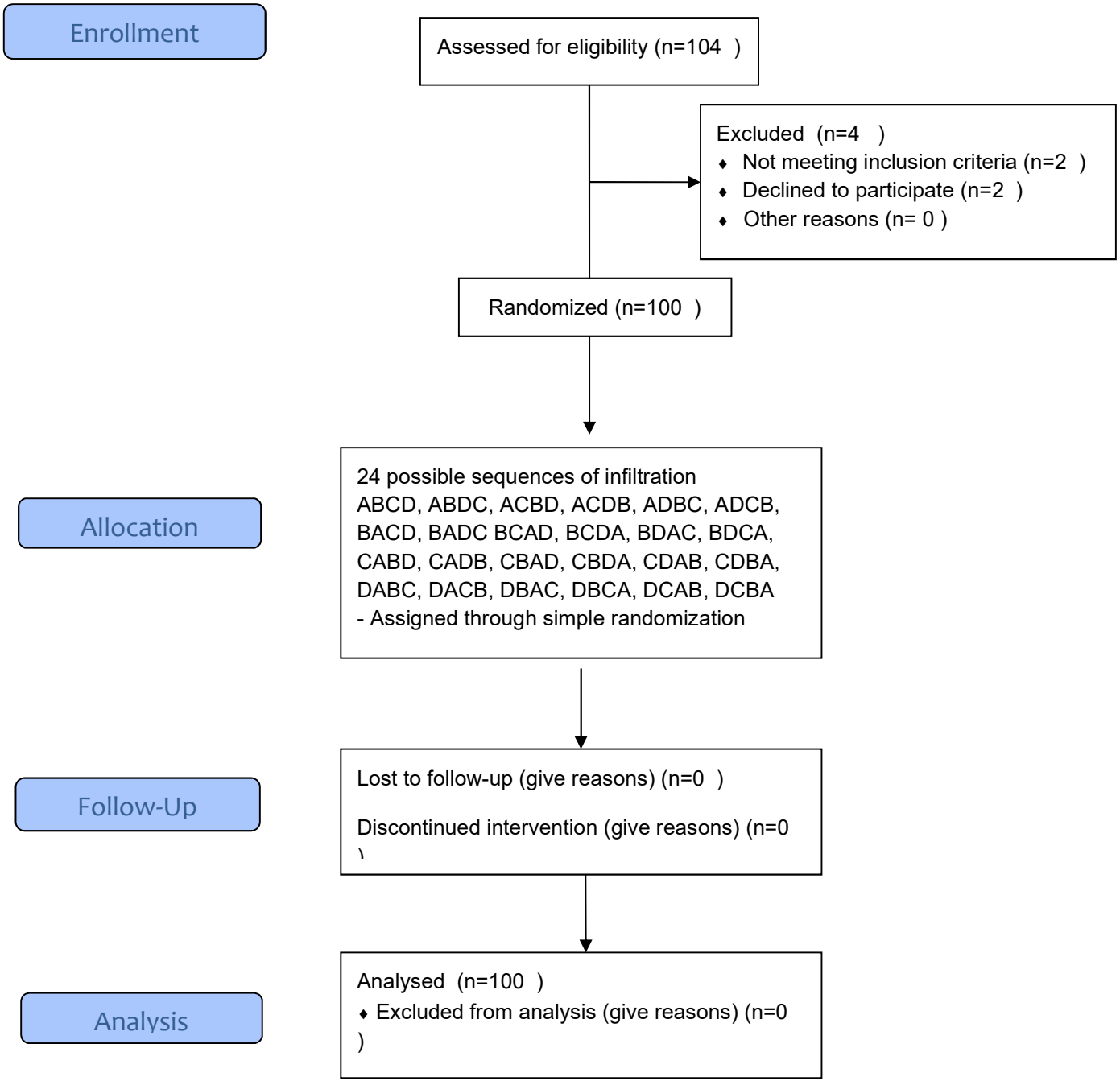
Any of the analgesic methods improves pain control respect to not utilizing any of them.

Our second aim is to evaluate if any of the analgesic methods evaluated achieves a better pain control than the others.

Randomization details

The sequence of infiltration zones of each subject was randomized through simple randomization, performed by the statistic department of the Medical Research Institute Hospital La Fe.

CONSORT Flow Diagram



Interim analysis

Performed by: Alberto Pérez-García

Date: 16/03/2019

An interim analysis was performed when 50 subjects had already been recruited. A sample size of 46 subjects (184 interventions) was estimated, assuming a variance in the values of the control zone of 2,69, with a precision of 1, confidence level of 95%, and statistical power of 0,9.

No modifications were performed to the protocol after the interim analysis.

Guidelines for stopping study early: None

Date of final analysis: 30/04/2019

No protocol deviations were detected

Intervention adherence was not necessary as no follow-up was required

Population analyzed

From the 100 healthy subjects included in the study, 61 were females and 39 males. The average age was 39,71 (sd 13,22).

Exclusion criteria

- Chronic pain syndromes/conditions
- Receiving opioid analgesics and sedatives
- Extreme sensitivity to cold
- Allergy to components of the anesthetic cream EMLA (eutectic mixture of lidocaine; 2,5% lidocaine and prilocaine 2,5%)
- Inability to understand the visual analogic scale

Inclusion criteria

Every subject that did not meet any of the exclusion criteria, and signed the informed consent, was included in the study

Recruitment strategy

Adult employees and volunteers at The University and Polytechnic Hospital La Fe that understood the study and signed the informed consent were eligible for participation.

We did not have any case of **withdrawal** from the study

Material and methods

This study is a randomized, controlled, simple-blind clinical trial, and it has been approved by the Ethics Committee of the Medical Research Institute Hospital La Fe. The study included 100 healthy volunteers, and it was performed at the University and Polytechnic Hospital La Fe, Valencia.

The procedures of the study consisted in the sequential performance of four injections of 0,1mL of physiologic saline (0,9%NaCl) in the forehead of each subject, 2cm above the eyebrows, with a 29G needle, after applying each one of the non-invasive analgesic methods studied in the trial, except for the control zone. The anesthetic method utilized in each part of the forehead of each patient was randomized through simple randomization. Injections always started from the right side of the forehead to the left. The non-invasive analgesic methods utilized were:

- Control zone (A): None
- Vibration (B): Application of the vibrating device on the skin below the injection site, before and during injection.
- Cold (C): Application of a bag of 50mL of frozen physiologic saline covered with a plastic glove on the injection site for 50 seconds prior to performing the injection.
- Anesthetic cream (D): Application of a uniform thickness of 2mm of the anesthetic cream EMLA covered with an adhesive transparent plastic dressing for 30 minutes, before injection.

Results were evaluated through surveys that included demographic data (initials, gender, age), a Visual Analogic Scale (VAS) with a maximum value of 10 and minimum of 0 for pain evaluation of each of the four injected zones of each subject. Also, two direct questions were included, one with the aim of determining the preferred method for each subject for future injections ("Which anesthetic technique would you prefer if you had to be injected again?"), and another to report discomfort related to the application of any of the anesthetic procedures ("Did any of the anesthetic methods cause you pain or discomfort?")

An interim analysis was performed when 50 subjects had already been recruited. A sample size of 46 subjects (184 interventions) was estimated, assuming a variance in the values of the control zone of 2,69, with a precision of 1, confidence level of 95%, and statistical power of 0,9. The statistical study included a Friedman test for evaluating the existence of differences between the average results of each different anesthetic method and control zones, and to evaluate the existence of differences in pain referred depending on the injection order, or the side of the forehead injected (central or lateral). After finding statistically significant differences between average pain referred with different techniques, paired comparisons were performed between each non-invasive anesthetic method with a Wilcoxon test. For comparison of average pain according to subject gender, a Mann-Whitney U test was utilized. Statistical analysis was performed by a researcher that did not participate in the practical part of the study (Alberto Pérez-García) utilizing the software SPSS.