The Effect of Vibration on Pain during Intravenous Injection of Propofol: A Randomized, Controlled, Single-blinded Study

Registered United States Food and Drug Administration (FDA) Clinical Trial (**NCT #03509857**)

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Background and Significance

Infusion of propofol during the process of inducing anesthesia can cause a fair amount of transient discomfort to patients while they are on the operating table. It is not uncommon for patients to cry out in pain. The investigators have noticed this first hand on numerous occasions and have wondered if there is a risk-free way to lesson the pain associated with propofol infusion.

This study will focus on the use of vibration analgesia to potentially reduce the pain associated with propofol infusion. Vibration is proposed to stimulate A-beta nerve fibers, which transmit information from vibration and touch which, according to the Gate Control Theory of Pain (Melzack and Wall 1965), inhibits signal transduction by A-delta and C fibers (Kakigi and Shibasaki 1992). Vibration has been demonstrated to be effective in decreasing pain during vaccinations, phlebotomy, and dental anesthesia (Baxter et al. 2011; Nanitsos et al. 2009).

In this study, we seek to evaluate the role of vibration in the reduction of discomfort associated with painful stimulus during anesthesia induction. Through this study, we hope to develop a comprehensive and cost-effective approach to minimize patient discomfort during anesthesia induction.

Study Design

The objective of this study is to evaluate the effectiveness of vibration as an analgesic during induction of anesthesia. It is our hypothesis that vibration will lessen the pain of propofol infusion.

Patients who are set to receive a propofol infusion as part of induction of general anesthesia during surgery will be recruited to participate in this study. All participating patients will be randomized following acquisition of consent for study participation to one of two intervention groups: 1) normal standard of care infusion of propofol without vibration analgesia 2) infusion of propofol with application of vibration analgesia prior to infusion. The amount of pain perceived by patients during the infusion will be analyzed via two methods: first the commonly utilized visual analogue scale (VAS) as well as the more objective four-point pain manifestation scale (J.-R. Lee et al. 2007, Grauers et al. 2002). Patients will be asked to place a mark on a 10-cm visual analogue scale corresponding to the level of pain that they experienced during the infusion, as commonly utilized in previous studies. Additionally, two trained study investigators (one blinded to treatment group) will document the subject's perceived maximum pain/discomfort using a four-point pain manifestation scale as outlined in previous pain studies: (1) "severe" pain if pain manifests as verbal response accompanied by facial grimacing or withdrawal of arm, (2) "moderate" pain if grimacing or arm withdrawal is not accompanied by verbal response, (3) "mild" pain if within 30 seconds, severe or moderate pain is not observed, the patient is asked whether they had any discomfort in the arms and they answer 'yes,' (4) "no"- pain if within 30 seconds, severe or moderate pain is not observed, the patient is asked whether they had any discomfort in the arms and they answer 'no.'

Due to constraints regarding the validity of the linear visual analogue scale in very young patients (Stinson et al. 2006), only adults who are able to consent for themselves will be eligible for participation in the study.

Exclusion criteria include minors and pregnant individuals.

The primary outcome will be the level of pain reported by the patient immediately following propofol injection, with or without a vibration analgesia adjunct. Secondary outcomes will include subgroup analysis for responses in pain as stratified by pathology, age, sex, and ethnicity.

Intervention

Patients will be randomized to one of two treatment groups. Randomization will be performed by placing equal numbers of indicators for each treatment group in opaque, sealed envelopes, which will be shuffled. The surgeon will have access to a kit which contains these envelopes. One card will be selected in sequence from the pre-shuffled stack for each patient who gives consent to participate in the study.

The intervention group will receive vibration only, with application of the BUZZY device just proximal to the intravenous infusion site immediately before and during propofol infusion. Propofol will be administered according to the institution's standard weight-based dosing (2 mg/kg) infused over 3 minutes, repeated as needed to achieve the desired sedation level.

Immediately following intervention, patients will be asked to rate the discomfort of the infusion on both a Numeric Rating Scale, with a number between 0 and 10, and a Visual Analogue Scale, by placing a mark on a continuous 10-cm line corresponding to their level of perceived pain. Additionally, two trained study investigators (one blinded to treatment group) will document the subject's perceived maximum pain/discomfort using a four-point pain manifestation scale as described in the above "Study Design" section. These values will be used to compare efficacy between each intervention arm as described in the Statistics section.

With regards to safety outcomes, no significant safety issues are anticipated beyond those inherent to established practice.

Response cards will not contain any identifiable patient information and will be linked to consent forms only through a numerical key. Consent forms will be stored separately in a secured in-hospital location following each patient interaction.

Intervention will be performed in the operating room during general anesthesia induction, as indicated, following acquisition of patient consent and randomization to a treatment arm as described above. Only a single intervention will be performed. Routine office follow-up will be offered to each patient for longitudinal management of any potential harms.

Population

Patients will be recruited from Montefiore Medical Center, Hutchinson ambulatory surgery center in the preoperative holding area prior to their surgery.

The study sample size will need to be approximately 100 patients, 50 in each treatment arm, to achieve a power of 80% to detect a difference of 10 mm on the Visual Analogue Scale between any two study arms. This was based upon a previous study (Nakayama et al. 2001) which demonstrated a mean reduction in discomfort between buffered and unbuffered lidocaine of 1.0 on the Numeric Rating Scale (from 3.5 to 2.5, with a SD of 1.4).

Given that the study involves a single interaction, there is no dropping out from the study or loss-to-follow-up anticipated.

Inclusion and exclusion criteria are described in the above sections. Specifically, however, minors may not be recruited into the study, as the Visual Analogue Scale is not considered reliable for that age group (please see Study Design section).

The consent form will be provided in English, and will be reviewed via translation phone for non-English-speakers, provided that the treating or examining physician is not fluent in the patient's preferred language.

No tissue specimens or blood samples will be obtained from participating patients. Recruitment

Patients will be recruited into the study by the surgeon prior to their operation. No additional recruitment materials will be utilized. The study will be explained in-person and consent obtained with appropriate documentation. Privacy will be protected by keeping the consent documentation in a separate, locked, secure location from the response cards.

Informed Consent

The informed consent form in use for this study is based upon the Einstein IRB recommended template and has been included with this study application.

Informed consent will be obtained in the preoperative holding area where the patient is spoken to by both the anesthesiologist and surgeon. Eligible patients will be given the opportunity to enroll in the study after it has been determined that they will receive propofol infusion as part of their general anesthesia.

If they prefer to forgo study participation, they will receive the Standard Treatment and will not be enrolled; no information from the encounter, except a running count of individuals who refused to participate, will be recorded for use in the study. There is no requirement for a waiver of informed consent.

This study will be performed without additional cost to participating patients and no renumeration will be offered for participation.

All enrolling physicians will be employees of Montefiore Medical Center or the New York City Health and Hospitals Corporation and will have received training in accordance to the Health Information Portability and Accountability Act.

Risks/Benefits

Risks associated with the BUZZY(tm) device

There are no known risks for the use of the BUZZY(tm) device, which is registered as an FDA class I device ("therapeutic massager").

Risks to privacy

The only identifiable patient information in this study will be the consent form, which will be linked to the corresponding response card by a numerical key. The consent forms will be collected daily and placed in a separate, secure location. No component of this study will be videotaped for research purposes.

Benefits

Patients who agree to participate in this study will be given the chance to receive an analgesic modality (vibration) to reduce the pain of local anesthetic injection. This is expected to reduce the discomfort of propofol infusion.

This study will benefit general practice by helping reduce pain with propofol infusions and become the new standard of care for its administration. There is a non-negligible cost associated with its use.

Statistical Methods
All data will be entered into a single SPSS database. ANOVA will be performed to

determine if significant differences are present between study groups in terms of demographic/injury characteristics and the primary outcome. Univariate analysis will be performed on the demographic and injury characteristic to determine if any of them have a significant effect on the primary outcome. If any individual characteristic is found to have a significant effect, multiple linear regression will be performed to control for potential confounders. Furthermore, a correlation coefficient will be utilized to assess the inter-rater agreement for the visual analog scale pain scoring between the two observers.

As no intervention in this study entails significant risk above that entailed by the standard-of-care, there is no plan for interim analysis or early termination of the study.

Since this investigation involves only a single patient interaction, there are no anticipated issues regarding loss-to-follow-up.

Data Quality Control
The primary data points for this study are the Visual Analogue Scale (VAS) and

Numerical Rating Scale (NRS) of pain, as reported by patients immediately following infusion of propofol as well as those perceived by study investigators as detailed above. The NRS, although not necessarily as reliable as the VAS, is a single whole number, which cannot be subject to interpretation by the examiner. The VAS is measured from a value of 0-10cm along a continuous line, and the patient is asked to place a mark on the line at a point at which, they feel, corresponds to the level of their pain. This value will be measured by a third, independent investigator not otherwise involved in the study.

Following acquisition of the NRS and VAS pain values, these values will be entered in the study database, which will be maintained solely by the primary investigators, keyed to individual participants' consent forms by a non-identifying serial number. Again, the consent forms will be stored in a separate location. Given the single site and relatively small size of study subjects, close monitoring by the study investigator is an adequate level of monitoring for this advice, as outlined and described in the DSM policy. 31 March 2018

All statistical analyses will be reviewed and verified with a faculty statistician.

Results

A total of 100 participants were recruited between April 2019 and November 2019, 50 in each study arm (control versus treatment group) with no losses or exclusions after randomization; recruitment was stopped once the calculated sample size was obtained. The control group and treatment group were comparable with respect to demographic characteristics. The mean age of patients was 50.8 ± 13.9 years. 39% of patients were males. The mean patient BMI was 28.5. Agreement between the attending anesthesiologist and CRNA observers regarding pain scores (scale from 0 to 3 points) was excellent and statistically significant, with weight kappa (κ_w) = 0.82 (p<0.001).

A significantly lower incidence of pain was found in the treatment group as compared to the control group. Nine (18.0%) patients in the treatment group had pain during propofol injection as compared to nineteen (38.0%) patients in the control group (p=0.03), yielding a risk difference of 20.0%. Significantly lower severity of pain was found in the treatment group as compared to the control group. The median summative pain score (scale: 1-6) in the treatment group was 1 [IQR: 1-2] as compared to 2 [IQR: 2-4] in the control group (p <0.01).

A higher incidence of pain with propofol infusion was noted in patients with an intravenous catheter location in the hand as compared to other locations with a risk ratio of 2.7 (95% CI:1.07-6.97, p=0.04). A log-binomial regression analysis was performed adjusting for the intravenous catheter location. A significantly lower incidence of pain in the treatment group versus the control group was maintained in the regression analysis with a risk ratio of 0.44 (95% CI:0.22-0.86, p=0.02).

The propofol dose did not differ significantly between the treatment and control groups and did not differ significantly in patients with or without pain (p=0.95 and p=0.30, respectively).

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