TITLE: The effect of pretreatment with intravenous lidocaine for intravenous contrast: A double-blinded, randomized-control trial

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INTRODUCTION

The management of pain is a key aspect of pediatric emergency medicine. Oftentimes, the pain is a result from medical procedures or interventions required in their treatment. Computerized tomography (CT) scans with intravenous (IV) contrast-media is a common procedure required to diagnose many common pediatric pathologies such as retropharyngeal abscess and appendicitis that can lead to discomfort and pain. Because of this discomfort and pain, pediatric patients are often unable to remain still during the infusion of IV contrast and require procedural sedation, which increases the patient's risk for adverse effects. The current standard of care involves no medication to prevent or mitigate IV contrast associated discomfort. This double-blinded, randomized controlled study attempts to determine if an infusion of IV lidocaine prior to IV contrast will reduce pain when compared to placebo.

BACKGROUND AND SIGNIFICANCE

The management of pain is a key aspect of pediatric emergency medicine that is not only complex but also difficult to assess.[1] Many times, the pain comes from the medical procedures or interventions required in their treatment.[2] Moreover, studies have shown that due to the neuroplasticity of neonates and infants, poorly controlled pain can lead to hypersensitivity to pain later in life.[3,4] It is therefore vital to identify methods and strategies to reduce pain in pediatric emergency care.

Intravenous contrast-media is a commonly used for CT scans for improved image clarity in pediatric emergency medicine. At times, IV contrast-media is required in order to clearly delineate such processes as retropharyngeal abscess or appendicitis. IV contrast-media has been associated with multiple immediate negative effects including nausea, vomiting, warmth at the site of administration, and pruritus during infusion as well as delayed responses, such as anaphylaxis and nephrotoxicity.[5-7] For the immediate reactions, these symptoms can be explained to many adults and adolescents; however, in the younger pediatric population especially under the age of 6 years old, it is difficult to explain and these symptoms, which can be perceived as frightening, uncomfortable, or painful. Children who feel discomfort during the administration of IV contrast media may not remain still during the CT scan, which affects the overall study quality and reliability. Therefore, many young patients often undergo procedural sedation in anticipation of movement artifact degrading the diagnostic accuracy. Procedural sedation, while a common procedure in the pediatric emergency department, does have significant complications, and it increases the risk of adverse events for the patient.[8,9] The risk of airway compromise associated with procedural sedation is particularly concerning in children requiring IV contrast for imaging of an upper airway pathology such as retropharyngeal abscess, as the disease itself narrows the airway. This presents the physician with a dilemma of assessing the extent of disease without the additional risk of airway compromise by using procedural sedation.

Previous research has looked at premedication with steroids prior to IV-contrast media administration to avert an allergic response.[10] However, there has been no investigation of premedication to abate the immediate adverse effects of discomfort associated with IV contrast injection. Propofol is a commonly administered medication in the emergency department known to cause pain at the injection site, the administration of which often includes pretreatment with intravenous lidocaine in order to mitigate the infusion's burning sensation.[11,12] The safety of IV lidocaine in pediatric patients has been documented in studies of its use for post-operative pain, using doses from 1.0 to 1.5 mg/kg with no known adverse side effects.[13,14] CT scans with IV contrast are performed on a near daily basis in the Maimonides pediatric

emergency department, usually for the assessment of acute appendicitis. The standard of care in children and adults receiving IV contrast does not include pre-medication to prevent IV contrast-associated discomfort. This double blinded prospective study aims to determine whether pre-treatment with lidocaine can mitigate the immediate discomfort of IV contrast in verbal children and adolescents who can comply with a pre and post IV contrast pain assessment. Moreover, this study also has the ability to be extrapolated to adult patients as the adverse effects of IV-contrast are similar. The aim of this investigation is to identify a pain-free experience for pediatric patients, obviating the need for sedation in younger patients, and improving the overall quality of care.

STUDY OBJECTIVES

- To improve patient's comfort during CT scans
- To promote and encourage "pain-free" emergency departments
- To develop a protocol to improve pediatric patients' compliance for CT scans without requiring procedural sedation

HYPOTHESIS

Pretreatment with intravenous lidocaine when compared to the placebo (normal saline) will reduce pain and discomfort after infusion of intravenous contrast media.

STUDY DESIGN

Subjects: Patients aged from 7 to 17 years-old who present to the Maimonides Medical Center's Emergency Department that require a CT scan with IV contrast. Research team members will be notified when the patient requires CT scan with IV contrast and meets the eligibility criteria. Potential subjects will be recruited in the Emergency Department

Eligibility Criteria: Inclusion criteria: Patients with age of 7 to 17 years-old who require a CT scan with IV contrast. Exclusion criteria: Patients with history of seizures, cardiovascular disease, presenting as a trauma, a history of anaphylaxis to lidocaine, or children/adolescents with underlying neurodevelopmental conditions which would interfere with their ability to respond to pre and post IV contrast pain assessments.

Design: This is a prospective, double-blinded randomized control study that will be comparing intravenous lidocaine to a placebo. Patients will be randomized with block randomization. The randomization list will be generated EM Research Manager and given to the EM pharmacist a priori of commencement of the study. The EM Research Manager and EM Pharmacist are not blinded to the study. Once a potential subject has been identified, a member of the research team will obtain consent from the parent or guardian of the subject. The research team member involved with consent and data collection, provider, and subject will all be blinded to which treatment arm they are assigned.

The research team members will monitor each patient and in conjunction with the pharmacy will deliver the assigned treatment to the subject's nurse to administer 10 min prior to the CT scan. If selected for the treatment group, the patient will receive a 1mg/kg IV dose of lidocaine with a max dose of 40mg.[15] A patient selected to the control group will an equal volume of normal saline infused. A research team member will be present during the administration of assigned treatment until the completion of the CT scan. The

patient will be placed on a cardiopulmonary monitor for the duration of this period. Advanced airway equipment, IV midazolam, and IV intralipids will also be available at bedside during infusion and until completion of CT scan to treat any potential adverse effect associated with lidocaine.

Nominal variables to be collected include gender, chief complaint, pain score at triage, use of pain medication at triage and during the ED course, diagnosis, type of CT scan performed, pre and post-intervention pain score, post-intervention pruritus score, post-intervention burning pain score. The only continuous variable being collected includes age (in years-old).

There will be no interruption or deviation from the standard of clinical care provided to each subject. This study will be run completely in the Pediatric Emergency Department.

Data Collection Procedures: Once a subject has been enrolled, the research team member will review the chart and collect all pertinent information as shown in the data collection template. A questionnaire will be completed prior to administration of the medication as well as following the CT scan which will be administered by the research team member. We will use a combination of the Baker-Wong FACES pain scale and 1 to 10 numerical scale for pain as well as a 5-point Likert scale for discomfort. Once all data has been collected, it will be recorded in password protected document located on a secure server only accessible to members of the research team. All information about the patients will be de-identified. Study investigators will record pain scores, vital signs, and adverse effects at prior to intervention, immediately following intervention, and 15 min following the intervention

The preparing ED pharmacist, research manager, and statistician will be the only ones with knowledge of the study arm to which each participant would be randomized. Treating providers, participants, and the data collecting research team will be blind to the medication route received.

All data will be recorded on data collection sheets, including patients' gender, demographics, medical history, and vital signs, and entered into SPSS (version 27.0; IBM Corp) by the research manager. Development of the randomization list, confirmation of written consent acquisition for all participants, and statistical analyses will be conducted by the research manager and statistician who will work independently of any data collection.

Patients will be closely monitored for any change in vital sings and for adverse effects during the entire study period (up to 120 minutes) by study investigators.

Data Analysis: Data analyses will include frequency distributions, paired t-test to assess a difference in pain scores within each group, and independent-sample t-test to assess differences in pain scores between the 2 groups at the various intervals. Mixed-model linear regression will be used to compare changes in pain numeric rating scale across time points. This will compensate for participants lost to follow-up and allow all patients' data to be analyzed on an intention-to-treat principle. For categorical outcomes (e.g., complete resolution of pain), a X^2 or Fisher's exact test will be used to compare outcomes at 30 minutes. Percentage differences and 95% confidence intervals between the treatment groups will be calculated for all time points with $P<0.05$ to denote statistical significance.

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