Study Protocol - intramuscular epinephrine as an adjunctive treatment for severe pediatric asthma exacerbation

Background: In the United States, as many as 1.6 million children present to emergency departments (EDs) each year with an acute asthma exacerbation. Despite extensive research and expert opinion panels, optimal management for severe asthma exacerbations has not been definitively established. Indeed, national guidelines recommend that adjunctive therapies should only be 'considered' given that there is limited or no evidence showing benefit of these therapies in these life-threatening situations.

Epinephrine is a non-selective sympathomimetic that has been used safely for decades. When administered subcutaneously (SQ), it produces bronchodilation within 5-10 minutes. In recent years, intramuscular (IM) administration has become the favored route for patients with anaphylaxis based on studies showing higher peak plasma concentrations with the IM route. Despite this evidence, national asthma guidelines continue to recommend the SQ route when epinephrine is used for severe asthma exacerbation as an adjunct to the primary therapy: inhaled β_2 agonists.

Randomized trials have shown that SQ epinephrine is equally effective compared to inhaled β_2 agonists for the treatment of asthma exacerbation in children. Notably, the combination of SQ epinephrine and nebulized β_2 agonists has not been demonstrated to be more effective in children. One major limitation of these studies is that they did not look specifically at severe asthma on its own. As a result, epinephrine in either form (SQ or IM) is very rarely used for asthma exacerbation and is not considered to be standard first-line therapy.

In summary, prior work in this area has two major flaws. First, previous studies have looked at epinephrine administered SQ and not the potentially superior IM route. Second, no study focused specifically on severe asthma. The latter is notable because markedly poor air entry is one of the hallmarks of severe asthma exacerbation. It is biologically plausible that inhaled treatments could be complemented and enhanced in this subgroup by a drug systemically delivered to the β_2 receptor.

Project Aim: To determine if intramuscular epinephrine is an effective adjunct to inhaled bronchodilators (β_2 agonists) for children with severe asthma exacerbation.

Hypothesis: IM epinephrine is an efficacious adjunct to inhaled bronchodilators (β_2 agonists) for children with severe asthma exacerbation.

Methods:

Study design: This is a repeated measures, parallel group, single-blinded randomized controlled therapeutic trial.

Study site: Kosair Children's Hospital emergency department

Eligible participants: The study population will be comprised of children age 6-17 years old who present to the ED with severe status asthmaticus as diagnosed by the treating provider and verified by peak expiratory flow rate (PEFR) of <60% of predicted prior to intervention or a clinical asthma score of 7 or greater.

Inclusion criteria

1. Age greater than 6 years and less than 18 years
2. Pre-existing diagnosis of asthma
3. Presenting to the ED with an asthma exacerbation

Exclusion criteria

1. History of chronic lung or upper airway disease other than asthma
2. History significant, uncorrected congenital heart disease or cardiac arrhythmia
3. History of thyroid disease, stroke, sickle cell disease, or renal disease
4. Systolic blood pressure greater than the 95th percentile for height, age, and gender
5. Impending respiratory failure
6. Allergy to epinephrine
7. Pregnancy
8. Weight < 20 kg

Screening procedures: Patients presenting to the ED for asthma exacerbation who meet the inclusion criteria will be considered for enrollment in the study. A brief form will be completed by a study investigator or research assistant to assess for eligibility.

To accurately ascertain predicted PEFR, height will be measured. PEFR testing will be performed by respiratory therapists (RT) in the ED once the patient is brought into a treatment room. The RT will also measure the clinical asthma score.

Girls who meet all of the other screening criteria will be asked if they have achieved menarche. If so, they will be asked to give a urine sample so that a pregnancy test can be performed.

Consent procedures: The study will be described in detail initially. If the parents and patient would like to participate, then a research member will discuss the informed consent and assent (if applicable) with the families and obtain signatures.

Baseline data: Once screened, consented, and enrolled, the following demographic data will be collected: birthdate, gender, race, time of arrival to the ED, details of any treatment by a referring provider, symptom type and duration (hours), time since last inhaled bronchodilator (minutes), time since systemic corticosteroids (minutes), number and type of inhaled bronchodilator treatments in the preceding 24 hours, all home medications, drug and food allergies, past medical history, number of hospital admissions for asthma over the prior 12 months, and number of ICU admissions over the child's lifetime. Initial temperature, respiratory rate, heart rate, blood pressure, and pulse oximetry will be recorded. Finally, height, PEFR, and CAS will be measured by the respiratory therapist (RT) immediately prior to the study intervention. Additionally, the subject's family will be asked to complete an Asthma Control Tool (ACT). The ACT is a measure of how well the participant's asthma has been controlled over the preceding three months.

Intervention: Subjects will then be randomly assigned (50% chance) to receive a weight based dose of IM epinephrine 1:1000 or no adjunctive medication. The dose will be 0.2 mg for subjects 20-30 kg and 0.3 mg for subjects greater than 30 kg. This will be injected intramuscularly by an ED nurse into the anterior thigh muscles of the subject using a 1 ml syringe and a 23 gauge one inch needle.

In addition to the study intervention, the standardized treatment pathway based on the current asthma guidelines in use at our center will be utilized. This pathway includes nebulized albuterol, ipratropium bromide, and systemic corticosteroids. The duration and dosages of these other interventions will be administered at the discretion of the treating provider.

Randomization: A block randomization scheme will be used to promote balance at the end of the study. Block randomization ensures that after each block of individuals are enrolled in the study (n individuals in total); an equal number of individuals will be assigned to each group (n/2 individuals in each group). We will use random block sizes of 8-12.

Allocation concealment: The RT will be blinded as to whether the subject receives a dose of IM epinephrine. Once a patient is determined to be eligible for the study, the research team will complete informed consent/assent. A pharmacy generated randomization schedule will be utilized and sealed envelopes with the allocations (treatment or control) will be kept in the charge nurse's office.

At the time of allocation, the charge nurse will instruct all staff to leave the subject's room. The charge nurse will then open the designated envelope and personally prepare and administer IM epinephrine if the subject is allocated to the treatment arm. If the subject is allocated to the control arm, the charge nurse will draw up a syringe with the appropriate amount of saline as if an injection of epinephrine was going to be given to the participant. The charge nurse will take this syringe into the subject's room, but not administer it. Instead, a 'sham' Band-Aid will be placed over the thigh of the subject. They will be instructed not to reveal to the RT, research team, or bedside nurse whether or not an injection was actually given. Participants and families will be similarly instructed. The RT will remain blinded throughout and will be responsible for measuring all PEFRs and CASs.

Having block sizes that are randomly determined, as well as having larger block sizes of 8-12 will help minimize a member of the research team or the RT guessing the allocation of the next participant and potentially biasing recruitment or assessment. To further assess blinding, at the conclusion of the study, we will ask the RTs to guess which group the subjects they assessed were in.

Study data: The following data will be measured at time points (t_{15}, t_{30}, t_{60}, t_{90}, and t_{120}) minutes following IM epinephrine or sham drug administration: PEFR (if able), CAS, heart rate, respiratory rate, and pulse oximetry. This data will also be recorded at the time of discharge or admission from the ED. Also recorded will be amount and timing of bronchodilator, anticholinergic, and corticosteroid therapy given. Additionally, any other therapies and interventions will be recorded (i.e. oxygen administration, assisted ventilation, magnesium sulfate administration, etc.). ED length of stay as well as disposition will be noted.

Primary outcome measure: Change in percent of predicted PEFR/CAS 15 minutes after the study intervention (t_{15}).

Secondary outcome measures:

1. Change in percent of predicted PEFR/CAS at t_{15}

2. Disposition
3. Change in percent of predicted PEFR/CAS at t_{30}, t_{60}, t_{90} and t_{120}
4. Change in percent of predicted PEFR/CAS at t_{30}, t_{60}, t_{90} and t_{120}
5. Change in respiratory rate at t_{15}, t_{30}, t_{60}, t_{90} and t_{120}
6. Change in heart rate at t_{15}, t_{30}, t_{60}, t_{90} and t_{120}
7. Need for supplemental oxygen at t_{60}, t_{90} and t_{120} (defined as a room air pulse oximetry of <93%)
8. Need for albuterol at t_{60}, t_{90} and t_{120}
9. Number of hours of albuterol therapy
10. ED length of stay

Statistical analysis plan: First straightforward tests for differences among the two groups of individuals will be performed. Analysis of Variance (ANOVA) techniques will be used to test for differences among continuous variables, while Kruskal-Wallis, Fischer's Exact Tests and Wilcoxon methods will be used to test for differences among categorical variables. To examine the outcomes of: (1) change in percent of predicted PEFR/CAS, (2) respiratory rate, (3) heart rate, (4) hours of albuterol therapy and (5) length of stay in the ED, separate mixed-effects general linear models will be developed for each outcome (five models will be developed). The two arms (IM epinephrine and no epinephrine) will be analyzed as fixed effects, and time (time since randomization) will be analyzed as a repeated measures effect. Traditional risk factors (e.g. age, gender, and ethnicity) will be incorporated as covariates during secondary analyses. All main effects and all two-way interaction effects will be investigated for significance from the mixed-effects models developed. Negative binomial regression and logistic regression techniques will also be used to evaluate (7) need for supplemental oxygen and (8) need for albuterol. Life table analysis and Kaplan-Meier techniques will initially be used to analyze the time-related variables (e.g., time to discharge). The Log-rank test will be used to test for differences among survival curves. In addition, Cox (proportional hazards) regression techniques will be developed to test for differences among groups as well as allow for adjustment for additional covariates and risk factors. Cox regression will allow us to investigate all potential main effects and interaction effects. All statistical analyses will be performed by a statistician who is blinded to the treatment allocation of the two groups.

Planned interim analysis: Interim analyses, reported to the data monitor will be performed at 6, 9 and 12 months after the first participant is randomized. A Lan-DeMets spending function approach will be used to monitor the need for early trial termination.

Power calculation: We will develop separate mixed-effects general linear models for each of the outcomes. For a sample size (n=54) the study has 81% power to detect a 12% main effect of each treatment for each outcome. The estimated power for detecting a 5% interaction effect is 32%. The total sample size required to achieve 80% power to detect an interaction effect, based on the full-factorial designed proposed, is n=1728; which is not a feasible number in which to recruit and enroll. In addition, we will develop Cox proportional hazards regression models to assess the association between group assignment and time related outcomes. For the anticipated sample size (n=54), this study has 80% power to detect a hazards ratio of 1.82 with two-sided α=0.05. Lastly, multiple logistic regression techniques will be utilized to assess

the association between group assignment and dichotomized outcomes. Using the dichotomized version of some outcomes, this study has 80% power to detect on odds ratio of 1.58 with a two sided α=0.05 (n=54). Therefore, we have more than sufficient numbers of participants in each comparison group.

We anticipate that less than 10% of all potential participants will drop out. Therefore, we will recruit a total of 60 individuals for the current study (n=30 per group). This is a feasible sample size for the research team to recruit and enroll in the current study. Power calculations were based on the anticipated total sample size (n=54) that will be available for complete analysis. Using a block randomization scheme (with random block sizes of 8-12), we anticipate that n=30 participants will be assigned to each group.

Recruitment plan: A team of medical student research assistants already in place in the ED will be utilized to help with identifying and consenting potential subjects. Moreover, a research assistant dedicated to the study will be recruiting. All children who present to the ED with an asthma exacerbation while an investigator is available will be screened for eligibility. Based on prior experience, an average of five eligible children will present weekly or 20 per month. If five (25%) of these are recruited monthly, recruitment will be completed in 12 months. If three (15%) are recruited monthly, recruitment will be completed in 20 months.

Risks and benefits:

IM epinephrine has been used for years for the treatment of anaphylaxis in the same doses that will be studied. Severe adverse events are exceedingly rare. These include: cardiac arrhythmia and inadvertent injection into the systemic circulation. The latter could cause a transient, but potentially dangerous increase in the subject's blood pressure. Having the entire study take place in a pediatric emergency department where experts in the management of acutely ill children are immediately available further mitigates this exceedingly small risk. There are transient and minor side effects including anxiety, headache, fear, and palpitations that pass quickly.

At the participant level, the investigators believe there is true clinical equipoise with IM epinephrine in severe asthma exacerbation. However, there is biologic plausibility for a systemic drug to help children whose airways are closed off from severe asthma exacerbation. If the treatment works, subjects who receive epinephrine will breathe better more quickly than if they hadn't received the treatment.

At the societal level, demonstrating the utility of a novel, readily available, inexpensive treatment for severe asthma exacerbation would have far reaching effects for literally hundreds of thousands of children.

Data safety monitoring plan: A knowledgeable physician (Dr. Keith Cross) who is not a co-investigator for this study will serve as the study's safety monitor of adverse events. He will review all clinically significant adverse events within 72 hours. Any clinical adverse events noted by the study personal or the clinical team (MD, RN, RT) will be reported to the monitor within 24

hours. All severe adverse events will be reviewed by the monitor as soon as possible and reported to the IRB within 3 business days.

Severe adverse events include the following: tissue necrosis at the site of injection, cardiac arrhythmia, inadvertent intravenous injection or any other adverse event possibly related to the study intervention that has significant, persistent, or life-threatening impact on a subject. Dr. Cross has the discretion to suspend parts of the protocol from further study, or to stop enrollment until IRB review of any significant adverse event(s) can be completed.

As a pediatric emergency medicine physician at Kosair Children's Hospital and assistant professor of pediatrics at the University of Louisville, Dr. Cross has sufficient experience to be the safety monitor for this protocol, understand the impact of adverse events, and provide recommendations to ensure subject safety.

Confidentiality: All study data will be kept in the PI personal locked office located within Kosair Children's Hospital or in a lockbox in a locked call room within the ED. The PI's office is located in a locked and secure main office within the hospital. All electronic data will be stored on an encrypted and password-protected computer. Any data kept in paper form will be stored in a locked filing cabinet in the PI's office.