Original Article

Epinephrine in Anaphylaxis: Higher Risk of Cardiovascular Complications and Overdose After Administration of Intravenous Bolus Epinephrine Compared with Intramuscular Epinephrine

Ronna L. Campbell, MD, PhD, M. Fernanda Bellolio, MD, MS, Benjamin D. Knutson, MD, Venkatesh R. Bellamkonda, MD, Martin G. Fedko, MD, MHA, MBA, David M. Nestler, MD, MS, and Erik P. Hess, MD, MSc *Rochester, Minn*

What is already known about this topic? Epinephrine administration for the management of anaphylaxis is challenging and associated with the risk of overdose and cardiovascular complications. There are no studies that directly compared the safety of various methods of epinephrine administration in the emergency management of anaphylaxis.

What does this article add to our knowledge? Our study systematically compared the risk of cardiovascular complications and overdose with various routes of epinephrine administration, which allows the estimation of prevalence of these events and demonstrates increased risk with intravenous bolus epinephrine.

How does this study impact current management guidelines? Our study supports current guidelines that recommend the initial use of intramuscular epinephrine and avoidance of intravenous bolus epinephrine except in extreme circumstances in the emergency management of anaphylaxis.

BACKGROUND: Epinephrine is the drug of choice for the management of anaphylaxis, and fatal anaphylaxis is associated with delayed epinephrine administration. Data on adverse cardiovascular (CV) complications and epinephrine overdose are limited.

OBJECTIVE: To compare rates of CV adverse events and epinephrine overdoses associated with anaphylaxis management between various routes of epinephrine administration among patients with anaphylaxis in the emergency department.

METHODS: This was an observational cohort study from April 2008 to July 2012. Patients in the emergency department who met diagnostic criteria for anaphylaxis were included. We collected demographics; route of epinephrine administration; trigger; overdose; and adverse CV events, including arrhythmia, cardiac ischemia, stroke, angina, and hypertension.

RESULTS: The study cohort included 573 patients, of whom, 301 (57.6%) received at least 1 dose of epinephrine. A total of 362 doses of epinephrine were administered to 301 patients: 67.7% intramuscular (IM) autoinjector, 19.6% IM injection, 8.3% subcutaneous injection, 3.3% intravenous (IV) bolus, and 1.1% IV continuous infusion. There were 8 CV adverse events and 4 overdoses with 8 different patients. All the overdoses occurred when epinephrine was administered IV bolus. Adverse CV events were associated with 3 of 30 doses of IV bolus epinephrine compared with 4 of 316 doses of IM epinephrine (10% vs 1.3%; odds ratio 8.7 [95% CI, 1.8-40.7], $P = .006$). Similarly, overdose occurred with 4 of 30 doses of IV bolus epinephrine compared with 0 of 316 doses of IM epinephrine (13.3% vs 0%; odds ratio 61.3 [95% CI, 7.5 to infinity], $P < .001$).

CONCLUSION: The risk of overdose and adverse CV events is significantly higher with IV bolus epinephrine administration. Analysis of the data supports the safety of IM epinephrine and a need for extreme caution and further education about IV bolus epinephrine in anaphylaxis. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:76-80)**

Key words: *Anaphylaxis; Drug-related adverse effects and adverse reactions; Epinephrine; Drug overdose; Emergency department*

Anaphylaxis is an acute systemic allergic reaction.[1] Epinephrine is the drug of choice for the management of anaphylaxis, and fatal anaphylaxis is associated with delayed epinephrine administration.[2-4] Although anaphylaxis is most commonly treated in the emergency department (ED), it can occur in any health care setting, which requires all health care providers to be familiar with and prepared for acute anaphylaxis management.[5,6] Accurate and safe administration of epinephrine for anaphylaxis is challenging due to the multiple possible routes of administration

Department of Emergency Medicine, Mayo Clinic, Rochester, Minn

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Corresponding author: Ronna L. Campbell, MD, PhD, Department of Emergency Medicine, Mayo Clinic, 200 First Street SE, Rochester, MN 55905. E-mail: campbell.ronna@mayo.edu.

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Abbreviations used
CABG- Coronary artery bypass grafting
CV- Cardiovascular
ECG- Electrocardiogram
ED- Emergency department
EMS- Emergency medical services
HCTZ- Hydrochlorothiazide
HLD- Hyperlipidemia
HTN- Hypertension
IM- Intramuscular
IV- Intravenous
MI- Myocardial infarction
OR- Odds ratio
SC- Subcutaneous

and different dosages, depending on the acuity of the presentation. In addition, epinephrine dosing for anaphylaxis can be confused with cardiac arrest dosages.[7] Although adverse cardiovascular (CV) complications are associated most frequently with intravenous (IV) epinephrine and occasionally with other routes of delivery, data are limited to case reports, and there are no studies that directly compared the safety of various methods of epinephrine administration.[4,7-12] We sought to determine if rates of CV adverse events and epinephrine overdoses associated with anaphylaxis management differ among various routes of epinephrine administration among patients who present to the ED with anaphylaxis.

METHODS

Study design

We conducted an observational cohort study of patients who presented to the ED from April 2008 through July 2012.

Setting and participants

This study was conducted at Mayo Clinic Hospital, Saint Marys campus ED, a tertiary care academic ED that has a patient volume of 73,000 annual patient visits, including both pediatric and adult patients of all ages. Patients who presented with anaphylaxis as defined per the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network diagnostic criteria were consecutively included. The Mayo Clinic Institutional Review Board approved the study protocol.

Data source

Patients were enrolled as part of an anaphylaxis registry that has been ongoing since 2008 at the Mayo Clinic Hospital, Saint Marys campus ED. Electronic medical records of all patients who provided research consent and who had any ED diagnosis that contained "allerg," "anaphy," or "sting," were reviewed. "Allerg" would capture diagnoses, for example, allergic reaction, and "anaphy" could capture diagnoses such as anaphylactic reaction or anaphylaxis. Those who met the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network diagnostic criteria for anaphylaxis were included in our anaphylaxis registry, as previously described.[13]

Variables

Variables collected included patient demographics, allergic triggers (based on suspected trigger at the time of ED evaluation), signs and symptoms, epinephrine dose and route of administration, and complications of epinephrine administration. All doses of epinephrine were studied, including self-administered, emergency medical system provider administered, doses administered in other health care settings before ED arrival, and doses administered in the ED or ED observation unit.

Outcome measures

The outcomes of interest were epinephrine overdose and adverse CV events associated with epinephrine, including arrhythmia, cardiac ischemia, stroke, angina, or hypertension (HTN). Epinephrine overdose was defined as a dose that exceeded the recommended dose in published anaphylaxis guidelines (0.01 mg/kg, with a maximum dose of 0.5 mg for intramuscular (IM) epinephrine and 100 μg given as an IV bolus).[1,14-16] For a complication to be attributed to the epinephrine dose, the signs and symptoms could not have been present before the epinephrine dose and the onset needed to be temporally related (within several minutes or noted on the next set of vital signs after epinephrine administration) to the dose of epinephrine. All the patients who received epinephrine in the ED were undergoing continuous cardiac monitoring in accordance with departmental monitoring expectations. HTN was classified as an adverse outcome if the systolic blood pressure was $\geq$180 mm Hg or the diastolic blood pressure was $\geq$120 mm Hg after but not before administration of epinephrine. Cardiac ischemia required a documented troponin T level elevation in the setting of symptoms suggestive of cardiac ischemia, such as chest tightness, pressure, or pain. Angina was defined as chest pressure, tightness, or pain without a troponin T level elevation. A stroke was defined as the onset of any new neurologic deficit.

Statistical analysis

We present continuous data as medians (interquartile ranges), and categorical data are presented as percentage and frequency of occurrence. We compared the cohort of patients who received epinephrine with those patients who did not, and we estimated the association between mode of epinephrine administration and outcomes of interest, including overdose and CV events. We present the results and show demographics by patient groups and analysis by doses administered. We assumed independence of the events because the patients were at risk with every single dose. Odds ratios (OR) with corresponding 95% CIs were calculated for each association. Exact logistic regression was used to estimate ORs, CIs, and *P* values if the outcome of interest was not observed in 1 of the groups. For the OR calculations, the IM autoinjector and IM injection were combined, and IV bolus was analyzed individually and in combination with IV continuous infusion. We elected to use ORs because these are valuable when events are rare and the relative risk cannot validly be estimated directly. We present the results of the CV events by patients and by events because 1 patient presented 2 CV events. A sensitivity analysis for subcutaneous (SC) injection epinephrine was performed, including SC in either group (362 doses), and there was no significant change in the outcomes, thus SC doses were not included in the calculation of ORs. Statistical analyses were performed by using JMP software, version 9.0 (SAS Institute Inc, Cary, NC).

RESULTS

The study cohort included 573 patients, of whom, 301 (57.6%) received at least 1 dose of epinephrine (Table I). Overall, 341 patients were women (60%) and the median age

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