

Original Article

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

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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 2014;■:■–■)

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

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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

*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 ≥ 180 mm Hg or the diastolic blood pressure was ≥ 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 (52.6%) received at least 1 dose of epinephrine (Table 1). Overall, 341 patients were women (60%) and the median age

TABLE I. Comparison of patient characteristics among patients who did and did not receive epinephrine

	All patients, no. (%) (n = 573)	Received epinephrine, no. (%) (n = 301)	No epinephrine, no. (%) (n = 272)	OR (95% CI)	P value
Demographics					
Women	341 (60)	172 (57)	169 (62)	0.8 (0.6-1.1)	.22
Age*	34.5 (18.6-51.5)	33.4 (18.8-49.0)	35.1 (18.7-54.6)		.21
Race					
African American	17 (3)	12 (4)	5 (2)	2.2 (0.8-6.4)	.13
Caucasian	504 (88)	261 (87)	243 (89)	0.8 (0.5-1.3)	.33
Asian	12 (2)	8 (3)	4 (1)	1.8 (0.5-6.1)	.32
Other	40 (7)	20 (7)	20 (7)	0.9 (0.5-1.7)	.74
Suspected trigger					
Food	206 (36)	116 (40)	90 (33)	1.3 (0.9-1.8)	.17
Medication	115 (20)	44 (15)	71 (26)	0.5 (0.3-0.7)	.0006
Venom	63 (11)	49 (16)	14 (5)	3.6 (1.9-6.7)	<.0001
Unknown	140 (24)	74 (25)	66 (24)	1 (0.7-1.5)	.93
Other	49 (9)	18 (6)	31 (11)	0.5 (0.3-0.9)	.02
Personal history					
Asthma	163 (28)	87 (30)	76 (28)	1 (0.7-1.5)	.80

*Data are median age (interquartile range), y.

TABLE II. Overdoses and adverse CV events associated with routes of epinephrine administration

	IM autoinjector, N (%) (n = 245)	IM injection, N (%) (n = 71)	SC injection, N (%) (n = 12)	IV bolus, N (%) (n = 30)*	IV continuous infusion, N (%) (n = 4)
Overdose	0	0	0	4 (13.3)	0
Adverse cardiovascular event					
Arrhythmia	0	0	0	1 (3.3)	0
Ischemia	0	1 (1.4)	0	3 (10.0)	0
Stroke	0	0	0	0	0
Angina (no ischemia)	1 (0.4)	0	0	0	0
HTN	2 (0.8)	0	0	0	0

n, No. doses of epinephrine; N, no. events.

*One patient presented with 2 CV events in the IV bolus group.

was 34.5 years (interquartile range, 18.6-51.5 years). A total of 362 doses of epinephrine were administered to 301 patients: 245 IM autoinjector (67.7%), 71 IM injection (19.6%), 30 SC injection (8.3%), 12 IV bolus (3.3%), and 4 IV continuous infusion (1.1%). There was no difference by sex, age, or race in the frequency of epinephrine administration (Table I). The patients who received epinephrine were more likely to have venom as a trigger (16% vs 5%; OR 3.6 [95% CI, 1.9-6.7], $P < .001$) and less likely to have a medication as a trigger (15% vs 26%; OR 0.5 [95% CI, 0.3-0.7], $P < .001$), or a trigger classified as other (6% vs 11%; OR 0.5 [95% CI, 0.3-0.9], $P < .02$) when compared with patients who did not receive epinephrine.

There were a total of 4 overdoses and 8 adverse CV events in 8 different patients (Tables II and III). All of the adverse CV events and overdoses occurred in adult patients. All overdoses occurred when epinephrine was administered as an IV bolus; there were no overdoses with IM, IV continuous infusion, or SC administration. The overdoses occurred in 4 different patients and were associated with 3 cases of cardiac ischemia and 1 case of arrhythmia. One patient experienced both arrhythmia and cardiac ischemia simultaneously, and 1 patient with an IV epinephrine overdose vomited but had no CV events. IM epinephrine administration

was associated with 1 case of cardiac ischemia, 1 episode of angina, and 2 cases of transient HTN (Table III).

Analysis of adverse events by comparing IM vs IV bolus only epinephrine (346 doses). Three of 30 IV bolus doses of epinephrine (10%) were associated with 4 CV events in 3 different patients compared with 4 of 316 IM epinephrine doses (1.3%) that were associated with adverse CV events. Thus, adverse CV events were significantly more likely with IV bolus epinephrine administration when compared with IM (OR 8.7 [95% CI, 1.8-40.7]; $P = .006$). Similarly, an overdose was more likely with IV bolus epinephrine (4 of 30 doses) when compared with IM (0 of 316 doses) (13.3% vs 0%; OR 61.3 [95% CI, 7.5 to infinity], $P < .001$). There were no deaths secondary to overdose or adverse CV events. Note, this group excluded the 12 SC doses.

Analysis of adverse events of IM versus IV (bolus plus continuous infusion) (350 doses). When adverse events secondary to all forms of IV epinephrine administration (IV bolus plus IV continuous infusion) were analyzed compared with IM epinephrine administration, similar results were obtained. Adverse CV events were significantly higher with the IV

TABLE III. Details of patients with epinephrine overdoses or adverse CV events

Age (y)/sex	Dose/route	Where administered	Adverse event	Pre-existing CV disease	Daily CV medications
52/F	1 mg/IV bolus	Postoperative area	Ischemia, overdose: the patient received medication after an outpatient surgical procedure and developed suspected anaphylaxis but was hemodynamically stable; she received 1 mg IV epinephrine bolus; an ECG showed ischemic changes; troponin T level was positive (peak, 0.77 ng/mL)	HLD	None
22/F	0.5 mg/IV bolus	EMS	Arrhythmia, ischemia, overdose: the patient developed difficulty swallowing, difficulty breathing, wheezing, and hypotension after taking a medication; she received a 0.5 mg bolus of epinephrine IV by EMS during transport; she immediately developed headache, chest pain, and ventricular tachycardia, and was briefly unresponsive; serial troponin T level tests showed a progressive rise in troponin T level (peak, 0.33 ng/mL)	None	None
39/F	1 mg/IV bolus	Outpatient infusion therapy	Ischemia, overdose: the patient developed anaphylaxis after receiving a mAb infusion; symptoms included hypoxia and hypotension; she received epinephrine 1 mg IV bolus and developed chest pain, ischemic ECG changes, and elevated troponin T level (peak, 0.40 ng/mL)	None	None
34/F	0.75 mg/IV bolus	ED	Overdose: the patient presented with severe oropharyngeal angioedema and respiratory distress after eating a food to which she was allergic; she initially responded to IM epinephrine and then developed severe symptom recurrence; a 0.75-mg bolus of IV epinephrine was given (verbally ordered as 0.75 mL of 1:10,000 epinephrine [75 µg]); however, she received 0.75 mg of 1:10,000 epinephrine; the patient vomited after this	None	None
76/F	0.4 mg/IM	ED	Ischemia: the patient used a 0.3-mg epinephrine autoinjector before ED arrival for throat swelling and difficulty breathing, which began after ingestion of an unknown trigger; in the ED, the patient was noted to have posterior oropharyngeal edema and received 0.4 mg of IM epinephrine; after this, she developed chest tightness; here troponin T level was elevated (peak, 0.07 ng/mL)	HTN, HLD, previous MI and CABG	Lisinopril, HCTZ, atenolol, lovastatin
74/M	—/IM autoinjector	Home	Angina: the patient self-administered a 0.3-mg epinephrine autoinjector for a bee sting and developed chest tightness that had resolved before ED arrival; serial troponin T level measurements were negative	None	None
58/F	—/IM autoinjector	ED	HTN: the patient received 0.3 mg epinephrine via autoinjector for hives, angioedema, and dyspnea after taking a medication; her blood pressure increased to 224/134 mm Hg and normalized after approximately 10 min	HTN, HLD	Lisinopril, Atorvastatin
46/M	—/IM autoinjector	Home	HTN: the patient self-administered 2 doses of 0.3 mg epinephrine via autoinjectors, before arrival, for throat tightness, lightheadedness, and shortness of breath in response to an unknown trigger; in the ED, he was hypertensive, with a maximum blood pressure of 189/103 mm Hg; he had no history of HTN	None	None

CABG, Coronary artery bypass grafting; ECG, electrocardiogram; EMS, emergency medical services; HCTZ, hydrochlorothiazide; HLD, hyperlipidemia; MI, myocardial infarction.

route (including both bolus and IV infusion) when compared with the IM route (9.7% vs 1.3%; OR 7.5 [95% CI, 1.6-35.3], $P = .01$) as well as the odds of overdose (11.8% vs 0%; OR 53.4 [95% CI, 6.5 to infinity], $P < .001$).

DISCUSSION

To our knowledge, this is the first study to systematically compare the risk of CV complications and overdose with various routes of epinephrine administration for anaphylaxis. We found a significantly higher risk of CV complications (10% vs 1.3%) and overdose (13.3% vs 0%) with IV bolus epinephrine compared with IM epinephrine administration. In addition, our results confirmed the relative safety of IM epinephrine administration. Although numerous case reports have established the link between IV bolus epinephrine and CV complications, and rare cases of CV complications with IM epinephrine have been published, our results provide a denominator and thus allow for an estimate of the prevalence of overdose and adverse CV events based on the total number of doses administered.^{4,7-12}

All of the CV complications associated with IV bolus epinephrine also were associated with an overdose. Based on published guidelines, IV bolus epinephrine should only be administered when a patient continues to be profoundly hypotensive despite multiple doses of IM epinephrine and IV fluid resuscitation, or has experienced cardiorespiratory arrest.¹⁷ Furthermore, the recommended dose is approximately 50 to 100 μg given slowly. Two of the 4 complications associated with IV bolus epinephrine in our study were secondary to doses of 1 mg IV, likely due to confusion with cardiorespiratory arrest doses of epinephrine. Both of these cases occurred before arrival in the ED (outpatient infusion therapy and a postoperative setting). These results underscore the importance of education of all health care providers regarding safe dosing of epinephrine for anaphylaxis. Methods to prevent inappropriate doses such as those suggested by Kanwar et al⁷ may be important not only in the ED but in all health care settings.

The 1 overdose that occurred in the ED was due to improper administration despite the appropriate bolus dose being ordered. Other case reports have demonstrated this mechanism of error as well.^{10,11} This patient was in imminent danger of airway obstruction. Her severe airway edema had recurred after administration of IM epinephrine, and an IV infusion was not rapidly available. In times of high stress, it is easy to confuse a dose in milliliters with milligrams, and, given that IV bolus epinephrine is rarely ordered outside of cardiac arrest situations in the ED, even the most experienced physicians and nurses can be unfamiliar with such dosing.

The complications associated with IM epinephrine in our cohort were relatively minor. Although there was 1 case of ischemia in an elderly person, an isolated troponin T level elevation of 0.07 ng/mL would be unlikely to result in significant long-term morbidity. However, rare case reports have shown that IM epinephrine can be associated with more severe CV outcomes, including intracranial hemorrhage and myocardial dysfunction.^{8,9} Although IM epinephrine administration is not without risk, these must be weighed against the risk of untreated anaphylaxis, which could result in CV collapse or airway obstruction.

Limitations

Our study has several limitations. Due to the retrospective design, data quality is dependent on the accuracy of the medical records, and it is possible that adverse outcomes could have occurred that were not documented. Transient HTN is frequently observed after epinephrine administration and might not always be recorded; however, the

clinical repercussions of transient asymptomatic elevations in blood pressure after epinephrine are not clear. Although there may have been inadvertent overdoses that were not documented, it is unlikely that major adverse events would have gone undocumented. Also, because of the small number of patients who experienced adverse events, we combined IM autoinjector with IM injection data and, therefore, cannot compare the safety of autoinjector administration with nonautoinjector IM administration of epinephrine. Due to the small number of patients who received an IV infusion of epinephrine, we also could not estimate the safety of the IV continuous infusion.

CONCLUSIONS

Our results underscore the risks associated with the use of IV bolus epinephrine in the management of anaphylaxis. Furthermore, they demonstrate the relative safety of the use of the IM autoinjector, given that overdose is much less likely with this design and that there were no associated major CV adverse events. When taken together, these findings support current guidelines that recommend initial use of IM epinephrine and avoidance of IV bolus epinephrine except in extreme circumstances.

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