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Epinephrine use in the emergency department for anaphylaxis management: Systematic review

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ABSTRACT

Our study's goal was to evaluate the usage of epinephrine in ED patients who experienced anaphylaxis. Evaluate the route of administration (intravenous, intramuscular, subcutaneous); determine whether epinephrine was used as an initial treatment to manage anaphylaxis; and determine whether there is a correlation between the dose used and the frequency of cardiovascular adverse events. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed in the conduct of this investigation. We located publications that addressed the use of epinephrine to treat ANA in the ED by searching PubMed, Scopus, and the Web of Science Core Collection. A language limitation was applied in order to include articles published in English. The publication date limitation was applied only to articles published between 2010 and 2024. To minimize the risk of missing any pertinent citations, we also thoroughly reviewed the reference lists of the original papers included. We found that the risk of overdosing and serious cardiovascular events is significantly increased when administering an intravenous adrenaline bolus. The results of this study supported the safety of intramuscular epinephrine and the need for more awareness and further instruction on IV bolus epinephrine in ANA patients. In order to manage anaphylactic responses, it is recommended that emergency department staff undergo educational training on proper epinephrine administration.

Keywords: Epinephrine, emergency department, anaphylaxis

1. INTRODUCTION

Anaphylaxis (ANA) is a severe, perhaps fatal systemic allergic reaction with an abrupt start that typically occurs after being exposed to an allergen. Food, hymenopteran venom, and medications are common causes of ANA (Sampson et al., 2006). ANA is a medical emergency that has to be identified and treated right away. The first-line therapy of choice is epinephrine (Muraro et al., 2014), and a major risk factor for deadly ANA is its delayed delivery (Muraro et al., 2014; Simons et al., 2015).

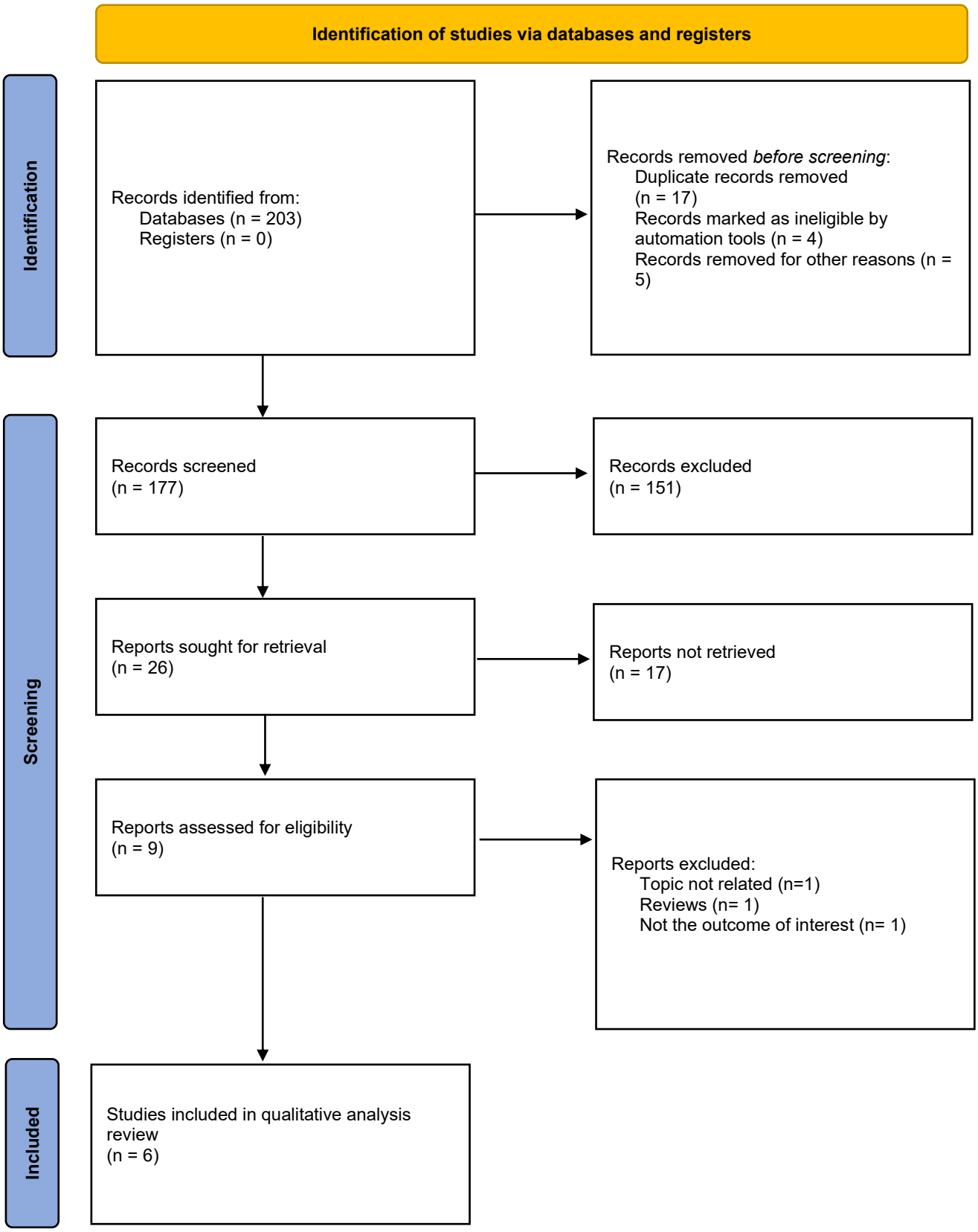

Fig 1: PRISMA consort chart of studies selection

One of the most frequent causes of ANA is drugs (Simons et al., 2015). Drugs were the leading cause of ANA-related fatalities according to a research by Jerschow et al., (2014). According to recent data, drug-induced anaphylaxis (DIA) occurs in about 0.03% of inpatients, with a 3–9% fatality rate. However, the majority of prior research evaluating the therapy of ANA has only included patients who present to outpatient allergy clinics (Cianferoni et al., 2001; Järvinen et al., 2008) or emergency departments (ED) (Brown et al., 2001). The use of epinephrine in individuals who acquired ANA in broad clinical settings has been the subject of very few investigations. Healthcare professionals must correctly handle anaphylactic patients in outpatient, hospital, and ED settings due to the prevalence and possible severity of ANA.

Therefore, the goal of our study was to evaluate the use of epinephrine in ED patients who experienced anaphylaxis (ANA). Evaluate the route of administration, intravenous (IV), intramuscular (IM), subcutaneous (SC); determine whether epinephrine was used and whether it was used as an initial treatment to manage ANA; and determine whether there is a correlation between the dose used and the frequency of cardiovascular (CV) adverse events linked to epinephrine.

2. METHOD

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. By searching PubMed, Scopus and the Web of Science Core Collection, we found papers that discussed the use of epinephrine to treat ANA in the ED. Terms from the controlled vocabulary were used where they were acceptable and accessible. To include papers published in English, a language constraint was used. Only papers released between 2010 and 2024 were included in the publication date restriction. We also carefully reviewed the reference lists of the included original publications to minimize the possibility of overlooking any relevant citations. We include 6 articles in our systematic review (Fig. 1).

Studies that documented the administration of epinephrine in the ED for ANA in a population of patients who arrived with ANA (medication-induced, food-induced, venom-induced, or any cause) were included in our analysis. English language publication, an observational study design, and a published paper were additional requirements for inclusion. Studies that failed to disclose the anaphylactic population's sample size, data collection period, patient questionnaires, or case reports were disqualified. Reviews, systematic reviews, meta-analyses, and intervention studies were also not included.

Title and abstract screening were carried out by two reviewers. Before proceeding to the official reviewing step, all reviewers discuss about queries and screened the titles and abstracts as a calibration exercise. Two reviewers independently reviewed each abstract and title to ensure it met the inclusion criteria. A third senior reviewer made decisions about titles and abstracts when there was dispute. Two reviewers independently evaluated each full text to ensure it met the inclusion criteria. When there was a debate about whole texts, the supervisor made a decision.

Data was separately retrieved from each entire text by two reviewers, and any differences were resolved. When necessary, we contacted the corresponding authors to clarify the data. The number of participants, study design, study purpose, key results and conclusion, and study duration were the primary outcome variables that we retrieved.

3. RESULTS

We included six articles in this review, which collectively involved a total of 1,870 patients. The study period ranged from 1 to 10 years (Table 1). 1.1% of patients underwent IV continuous infusion, 19.60% IM injection, 8.30% SC injection, 3.30% IV bolus, and 67.70% IM autoinjector, according to Campbell et al., (2014). Eight CV adverse events and four overdoses occurred in eight different individuals. Each overdose occurred during an IV epinephrine bolus. Adverse CV events were associated with 3 of 30 IV bolus epinephrine doses, compared to 4 of 316 IM epinephrine doses. Similarly, 0 out of 316 IM doses of epinephrine caused overdose, although 4 out of 30 IV bolus doses did.

According to Wang et al., (2017), the primary causes of drug-induced ANA were chemotherapeutic drugs, radiocontrast agents, antibiotics, and traditional medicine injections. Only 59.50% of patients received epinephrine treatment. Patients who took epinephrine were more likely to experience wheezing and respiratory arrest. Among patients with a complete record of the mode of administration, the proportion of patients who got epinephrine by IV bolus injection, SC injection, IM injection, or IV infusion was 16, 31, 43, and 8%, respectively. Of the 427 patients who had records of both the dosage and the administration mode, an IV bolus was more likely to cause an overdose (94%) than an IM injection or SC injection.

The criteria-confirmed anaphylactic group in the Meir et al., (2022) research had the following presenting signs and symptoms, in decreasing order of frequency: gastrointestinal, CV, respiratory, and mucocutaneous. The criteria-confirmed anaphylactic group was

more likely to have had prior ANA, pre-ED or ED epinephrine administration, and allergy referral. Tryptase levels were only observed once in the group with criteria-confirmed ANA and never in the group without; they were rarely present. Despite the low death rate, 64% of the criteria-confirmed anaphylactic samples required hospitalization, with 23% admitted to an intensive care unit. The main findings of the included studies were presented in Table 2.

Table 1: Main characteristics of the included studies

Citation	Study design	Sample size	Study period
Campbell et al., 2015	Observational cohort	573	4 years
Wang et al., 2017	Observational retrospective	427	10 years
Asai et al., 2014	Observational retrospective	98	1 year
Meir et al., 2022	Observational retrospective	82	1 year
Banerji et al., 2010	Observational retrospective	295	5 years
Clark et al., 2019	Observational, retrospective	459	2 years

Table 2: Findings of the included studies

Citation	Main findings
Campbell et al., 2014	From the total study sample, 1.1% received IV continuous infusion, 19.60% IM injection, 8.30% SC injection, 3.30% IV bolus, and 67.70% IM autoinjector. Eight separate patients experienced four overdoses and eight CV adverse events. Every overdose happened when an IV bolus of epinephrine was given. Compared to 4 of 316 doses of IM epinephrine, adverse CV events were linked to 3 of 30 IV bolus epinephrine doses. In a similar vein, 4 out of 30 IV bolus doses of epinephrine resulted in overdose, but 0 out of 316 IM doses did the same.
Wang et al., 2017	Antibiotics, radiocontrast agents, injections of traditional medicine, and chemotherapy medications were the main causes of drug-induced ANA. Just 59.50% of patients were treated with epinephrine. Wheezing and respiratory arrest were more common in patients who received epinephrine. The percentage of patients who received epinephrine via IV bolus injection, SC injection, IM injection, or IV infusion was 16, 31, 43, and 8%, respectively, among those who had a complete record of the method of administration. Compared to IM injection or SC injection, an IV bolus was more likely to result in an overdose (94%) among the 427 patients who had records of both the delivery method and the dosage.
Asai et al., 2014	In over 60% of instances, the apparent trigger was food. In nearly half of moderate-to-severe instances, no epinephrine was given, and a comparable proportion of patients with moderate-to-severe responses were not given an epinephrine auto injector (EAI) prescription. More severe responses were linked to shellfish exposure. Epinephrine was less frequently used to treat older patients and those not on steroids.
Meir et al., 2022	The presenting signs and symptoms for the criteria-confirmed anaphylactic group were gastrointestinal, CV, respiratory, and mucocutaneous, in decreasing order of frequency. Prior ANA, pre-ED or ED epinephrine treatment, and allergy referral were more common in the criteria-confirmed anaphylactic group. Seldom were tryptase levels arranged; they only happened once in the group with criteria-confirmed ANA and never in the group without. 64% of the criteria-confirmed anaphylactic sample needed hospitalization, with 23% admitted to an intensive care unit, despite the low fatality rate.
Banerji et al., 2010	Epinephrine, corticosteroids, antihistamines, and inhaled albuterol were administered to anaphylactic patients in the ED. Overall, 17% of patients who got epinephrine for food-related ANA received more than one dosage throughout their response. Just 10% of hospitalized patients with ANA had ANA listed as a diagnosis at release. 39% of patients

	were administered self-injectable epinephrine at the time of ED discharge, and 18% were referred to an allergist. 17% of epinephrine-treated ED patients with food-related ANA received more than one dosage.
Clark et al., 2019	Over time, more patients with ANA received epinephrine treatments in the ED. While advice to avoid the problematic allergen did not vary considerably, prescriptions for EAI upon discharge and paperwork for referral to an allergist/immunologist almost quadrupled. Although it remained low, the number of guidelines received nearly doubled throughout the research period.

4. DISCUSSION

In this study, we looked into the use of adrenaline to treat ANA in EDs caused by food and other causes. The risk of CV problems and overdose with different methods of epinephrine administration for ANA is thoroughly compared by Campbell et al., (2014). Comparing IV bolus epinephrine treatment to IM epinephrine administration, they discovered a markedly increased risk of CV problems and overdose. They also verified the relative safety of administering epinephrine IM. Rare instances of CV issues with IM epinephrine have been documented, despite the fact that several case studies have demonstrated the connection between IV bolus epinephrine and CV difficulties (Kanwar et al., 2010; Levis et al., 2011; Pumphrey, 2000).

IV bolus epinephrine should only be used when a patient has had cardiorespiratory arrest (CRA) or remains significantly hypotensive after receiving many doses of IM epinephrine and IV fluid resuscitation, according to published recommendations (Simons et al., 2015). Additionally, a gradual administration of 50 to 100 mg is advised. Due to possible misunderstanding with dosages of epinephrine used for CRA, two of the four problems linked to IV bolus epinephrine in Campbell et al., (2014) research were related to doses of 1 mg IV. Prior to arriving at the ED, both of these incidents took place. These findings underscore the importance of training all medical professionals in the safe administration of epinephrine to treat ANA.

Since delayed delivery has been demonstrated to lead to poor outcomes and death, epinephrine should be given as a first-line therapy to patients experiencing ANA (Campbell et al., 2014). Antihistamines (Choo et al., 2010; Sheikh et al., 2007) and corticosteroids (Campbell et al., 2014; Choo et al., 2010) are ineffective in treating acute ANA. According to Wang et al., (2017) data, only 74.1% of patients received epinephrine as their first therapy, indicating a low rate of utilization and inappropriate timing of administration. Patients with respiratory symptoms are more likely to receive epinephrine from clinicians.

Regarding the route of epinephrine administration, there is a notable disparity between the guidelines (Muraro et al., 2014; Simons et al., 2015). IM injection of epinephrine into the anterolateral thigh produces a higher and faster peak plasma concentration than SC injection in the arm (Simons et al., 1998), according to a prior pharmacokinetic study in children who are not experiencing ANA (Muraro et al., 2014). For this reason, IM should be the preferred route of administration. Only individuals who are not responding to IM injections should get an IV continuous infusion of epinephrine (Muraro et al., 2014). However, Wang et al., (2017) data indicated that continuous infusion was the initial method of epinephrine delivery in 8.1% of instances.

There are many limitations to our investigation. Because the included studies were retrospective in nature, the quality of the data depends on the accuracy of the medical records, and unrecorded negative events may have occurred. Although temporary asymptomatic blood pressure rises following epinephrine injection are commonly observed and may not always be documented, it is unclear what the therapeutic implications of these events are. It is doubtful that significant adverse outcomes would have gone unreported, even if there could have been unreported accidental overdoses.

5. CONCLUSIONS

Administering an IV bolus of adrenaline has a far higher risk of overdose and severe CV events. Studies have confirmed the safety of IM epinephrine and emphasized the need for heightened vigilance and additional training regarding IV bolus epinephrine in cases of anaphylaxis (ANA). It is advised that ED personnel receive educational training on how to administer epinephrine appropriately to treat anaphylactic reactions.

List of abbreviations

ANA, anaphylaxis

DIA, drug induced anaphylaxis

ED, emergency department
FIA, food-induced anaphylaxis
EAI, epinephrine auto injector
IM, intramuscular
IV, intravenous
CV, cardiovascular
SC, subcutaneous
PRISMA, The Preferred Reporting Items for Systematic reviews and Meta-Analyses

Informed consent
Not applicable.

Ethical approval
Not applicable.

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Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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