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[Intervention Review]

Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock

Aziz Sheikh¹, Yasser A Shehata², Simon GA Brown³, F Estelle R Simons⁴

¹Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, UK. ²Division of Community Health Sciences: GP section, The University of Edinburgh, Edinburgh, UK. ³Department of Emergency Medicine, The University of Western Australia at Fremantle Hospital, Fremantle, Australia. ⁴Department of Pediatrics & Child Health; Department of Immunology, Faculty of Medicine, University of Manitoba, Winnipeg, Canada

Contact: Aziz Sheikh, Asthma UK Centre for Applied Research, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, UK. Aziz.Sheikh@ed.ac.uk, asheikh2@partners.org.

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ABSTRACT

Background

Anaphylaxis is a serious hypersensitivity reaction that is rapid in onset and may cause death. Adrenaline is recommended as the initial treatment of choice for anaphylaxis.

Objectives

To assess the benefits and harms of adrenaline (epinephrine) in the treatment of anaphylaxis.

Search methods

In the previous version of our review, we searched the databases until March 2007. In this version we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 11), MEDLINE (1966 to November 2010), EMBASE (1966 to November 2010), CINAHL (1982 to November 2010), BIOSIS (to November 2010), ISI Web of Knowledge (to November 2010 and LILACS (1982 to November 2010). We also searched websites listing ongoing trials and contacted pharmaceutical companies and international experts in anaphylaxis in an attempt to locate unpublished material.

Selection criteria

We included randomized and quasi-randomized controlled trials comparing adrenaline with no intervention, placebo or other adrenergic agonists were eligible for inclusion.

Data collection and analysis

Two authors independently assessed articles for inclusion.

Main results

We found no studies that satisfied the inclusion criteria.

Authors' conclusions

Based on this review, we are unable to make any new recommendations on the use of adrenaline for the treatment of anaphylaxis. Although there is a need for randomized, double-blind, placebo-controlled clinical trials of high methodological quality in order to define

the true extent of benefits from the administration of adrenaline in anaphylaxis, such trials are unlikely to be performed in individuals with anaphylaxis. Indeed, they might be unethical because prompt treatment with adrenaline is deemed to be critically important for survival in anaphylaxis. Also, such studies would be difficult to conduct because anaphylactic episodes usually occur without warning, often in a non-medical setting, and differ in severity both among individuals and from one episode to another in the same individual. Consequently, obtaining baseline measurements and frequent timed measurements might be difficult, or impossible, to obtain. In the absence of appropriate trials, we recommend, albeit on the basis of less than optimal evidence, that adrenaline administration by intramuscular (i.m.) injection should still be regarded as first-line treatment for the management of anaphylaxis.

PLAIN LANGUAGE SUMMARY

Adrenaline for the emergency treatment of anaphylaxis

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. It is commonly triggered by a food, insect sting, medication, or natural rubber latex. The reaction occurs without warning and can be a frightening experience for those at risk and for their families and friends. Adrenaline (epinephrine) is widely advocated as the main treatment in those individuals experiencing anaphylaxis. There is no other medication with a similar effect on the many body systems that are potentially involved in anaphylaxis. The evidence base in support of the use of adrenaline is unclear. We therefore conducted a systematic review of the literature searching key databases for high quality published and unpublished material on the use of adrenaline for emergency treatment; in addition, we contacted experts in this area and the relevant pharmaceutical companies. Our searches retrieved no randomized controlled trials on this subject. We concluded that the use of adrenaline in anaphylaxis is based on tradition and on evidence from fatality series in which most individuals dying from anaphylaxis had not received prompt adrenaline treatment. Adrenaline appears to be life saving when injected promptly, however, there is no evidence from randomized controlled trials for or against the use of adrenaline in the emergency treatment of anaphylaxis. Given the infrequency of anaphylaxis, its unpredictability and the speed of onset of reactions, conducting such trials is fraught with ethical and methodological difficulties.

BACKGROUND

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (Sampson 2006). Trigger factors include foods, insect venoms, medications, anaesthetics, natural rubber latex, and exercise (Brown 2001; Brown 2004a; Kemp 2002; Lieberman 2003; Sampson 2005; Simons 2002a; Simons 2007a; Simons 2007b). Most anaphylactic episodes involve an immediate hypersensitivity reaction following allergen interaction with cell-bound immunoglobulin E (IgE). Less commonly other immunologic mechanisms, for example autoimmune mechanisms, are involved; or no immune mechanism is involved, for example when anaphylaxis is triggered by exposure to cold air or water. Some individuals have idiopathic anaphylaxis with no obvious trigger. Regardless of the inciting mechanism, the final common pathway involves release of histamine and other mediators from mast cells and basophils. Distinction between anaphylactic reactions and an anaphylactoid reaction is no longer recommended as the clinical picture and emergency treatment of anaphylaxis are similar regardless of the pathophysiologic mechanism (Johansson 2001; Johansson 2004; Sampson 2006; Simons 2007a).

Anaphylaxis is not a reportable disease and the true incidence is unknown (Bohlke 2004; Hebling 2004; Klein 1995; Lieberman 2006; Neugut 2001; Peng 2004; Sheikh 2001). An estimate of the incidence in the general population is influenced by definitions, which differ from one investigator to another, as well as by coding issues and misclassification errors (Clark 2006). A population-based study using data collected in the mid-1980s calculated an annual incidence of 30 per 100,000 person years, which raised concern that anaphylaxis was frequently not recognized (Yocum 1999). Other studies suggest the true incidence may be up to 590 per 100,000 person years. Anaphylaxis from the four most common triggers (foods, insect stings, medications, and natural rubber latex) may affect more than 1% of the general population (Neugut 2001) with considerable variations in age (Simons 2002a) and in age-specific aetiology (Alves 2001).

Skin symptoms and signs, including generalised urticaria, flushing, itching, and angioedema (swelling of the subcutaneous tissues), are the most common manifestations of anaphylaxis (in 90% of those affected) followed by respiratory (70%) and gastrointestinal (40%) symptoms; hypotension occurs in 10% to 30% (Brown 2001; Brown 2004b; Kemp 2002; Lieberman 2003; Simons 2002b). Symptoms often occur within five to 30 minutes of exposure to the trigger factor, although occasionally they do not develop for several hours. Anaphylaxis may be fatal within minutes, usually through cardiovascular or respiratory compromise, or both (Bock 2007; Greenberger 2007; Pumphrey 2000; Pumphrey 2007). Upper and lower respiratory tract obstruction is commonly reported in fatal cases (Bock 2007; Greenberger 2007; Pumphrey 2007). True mortality rates are unknown in anaphylaxis because of under-recognition and under-diagnosis of the disease (Pumphrey 2000).

The diagnosis of anaphylaxis is based largely on history and physical findings. Laboratory tests have proven to be disappointing in clinical practice. Plasma histamine may be elevated, but it is only reliable when measured within one hour of onset and the levels are not stable during routine handling, so it is seldom used (Lin 2000). Serum or plasma tryptase levels greater than 15 ng/mL within 12 hours (preferably within three hours) of the onset of an episode is more widely used as a confirmatory test, but this test is

usually negative in food-induced anaphylaxis. Serial total serum or plasma tryptase measurements may be more helpful than single measurements (Brown 2004a). Positive skin tests to allergens and elevated allergen-specific IgE levels in serum are not diagnostic of anaphylaxis. Rather, such tests confirm sensitization and provide clinically relevant information that directs risk reduction and the prevention of future episodes by avoidance of specific allergen or allergens; or long-term immunomodulation where relevant, for example with venom immunotherapy for insect sting anaphylaxis (Simons 2007a).

Adrenaline (epinephrine) is widely advocated as the initial treatment of choice for anaphylaxis (Alrasbi 2007; McLean-Tooke 2003; Simons 2004). This initial emergency management is supervised by a physician or other healthcare professional when anaphylaxis occurs in a healthcare setting. In this setting intramuscular (i.m.) or intravenous (i.v.) infusion, or both, routes for adrenaline are preferred (Brown 2006). When anaphylaxis occurs in the community, in a non-medical setting, the standard of first-aid treatment is the administration of self-injectable adrenaline into the anterolateral thigh using an EpiPen, Anapen, AnaHelp, Fastject, Twinject, or other adrenaline formulation (Sicherer 2005; Simons 2004).

Adrenaline is an alpha- and beta-adrenergic agonist (that is it acts on two different important classes of receptors in the body) with bidirectional cyclic adenosine monophosphate-mediated pharmacologic effects on target organs and a narrow therapeutic index (Simons 2006). It results in vasoconstriction, increased peripheral vascular resistance, decreased mucosal oedema, inotropic and chronotropic effects (increased force and rate of cardiac action), bronchodilation, and decreased mediator release from mast cells and basophils. The plasma and tissue concentrations of adrenaline needed for recovery from anaphylaxis have not yet been defined in humans (Simons 2004). There have been no prospective human studies performed during the management of anaphylaxis to evaluate the bioavailability and optimal dose of adrenaline given intramuscularly or to assess the incidence of adverse effects (Simons 2008). Case reports and large mortality reviews indicate that side effects involving the myocardium can be serious, usually in the setting of inappropriate dosing (an overdose, an inadequately diluted intravenous dose, or an overly rapid rate of infusion) by medical staff (Pumphrey 2000). However, there is now increased awareness that the heart itself may be a target organ in anaphylaxis and that electrocardiographic changes suggesting ischaemia, myocardial failure, and dysrhythmias can occur even if adrenaline has not been given (Brown 2005; Kounis 2006; Marone 2004).

Only the intravenous route was used in the two studies in humans that indicate a beneficial treatment effect for reactions characterised by cardiovascular collapse (Brown 2004b; Fisher 1978). In a canine model of fully-developed anaphylactic shock (defined as hypotension with the blood pressure contained at 50% of baseline blood pressure), adrenaline 0.01 mg/kg injected by the intramuscular route was ineffective; an intravenous bolus of 0.01 mg/kg resulted in transient improvement; and intravenous infusion at 0.19 to 0.45 µg/kg/min was the only method to produce a sustained improvement (Bautista 2002; Mink 2004). The therapeutic effect in this model was from positive inotropy, with no increases in either systemic vascular resistance or pulmonary arterial wedge pressure. Thus, if a severe reaction develops

and adrenaline is administered at the generally recommended initial doses for anaphylaxis, which are lower than the doses recommended for resuscitation, it might not adequately counteract the effects of vasodilation and distributive-hypovolaemic shock on its own, even when given as an intravenous infusion (Brown 2005).

In summary, the use of adrenaline in anaphylaxis appears to be based largely on extrapolation from first principles, expert opinion, and tradition.

OBJECTIVES

To assess the benefits and harms of adrenaline in the treatment of anaphylaxis.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomized controlled trials comparing adrenaline with no intervention, placebo, or other adrenergic agonists. We also planned to include randomized controlled trials comparing different approaches to the administration of adrenaline and quasi-randomized controlled trials, that is trials where an attempt to approximate randomization was made (for example by alternate allocation). Controlled trials with little attempt to minimize bias during allocation were, however, not eligible for inclusion.

Types of participants

We were interested in all patients (infants, children and adults; community or hospital based) experiencing anaphylaxis caused by food, insect venom, medication, vaccination, latex, or any other trigger.

Types of interventions

We were interested in studies involving any systemic (intravenous infusion or bolus injection, intramuscular, subcutaneous, or inhaled from a metered-dose inhaler or a nebulizer) administration of adrenaline by the individual, a lay caregiver (of a child), or a medical professional. Adrenaline could have been administered anywhere in the community, including in a physician's office or an ambulance; or anywhere in the hospital, including emergency departments, hospital clinics, dialysis units, wards, operating rooms, and delivery rooms. It may also have been administered after another medication. The comparative treatments of interest were no intervention, placebo, other adrenergic agonists; and different treatment approaches to the administration of adrenaline.

Types of outcome measures

Our outcome measures of interest were the following.

Primary outcomes

Death

Secondary outcomes

1. Resolution of upper airway obstruction
2. Resolution of lower airway obstruction (symptomatic bronchospasm)

3. Improvement in arterial blood pressure (greater than 50 mm Hg systolic)
4. Resolution of urticaria
5. Requirement for second dose of adrenaline
6. Admission to hospital
7. Length of emergency department stay
8. Length of hospital stay
9. Re-presentation for therapy within 24 hours
10. Adverse events due to therapy, in either treatment arm

Search methods for identification of studies

Electronic searches

In the previous version of our review, we searched all the databases until March 2007.

In this updated version we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 11) (see Appendix 1); MEDLINE (1966 to November 2010, Appendix 2); EMBASE (1966 to November 2010, Appendix 3); CINAHL (1982 to November 2010, Appendix 4); BIOSIS (1969 to November 2010, Appendix 5); ISI Web of Science (1956 to November 2010, Appendix 6); and LILACS (1982 to November 2010), Appendix 7).

We searched MEDLINE using Ovid with the Cochrane randomized controlled trial filter (Higgins 2009) and the following key words: anaphyl* and adrenaline. We adopted our search terms for other databases. We did not apply any language restriction.

Searching other resources

In an attempt to uncover any additional relevant published data, grey literature, unpublished data, and research in progress, we:

- contacted international experts in anaphylaxis (see Appendix 8);
- contacted relevant pharmaceutical companies (see Appendix 8);
- searched the UK's National Research Register: <https://portal.nihr.ac.uk/Pages/NRRArchive.aspx>
- searched websites listing ongoing trials: <http://clinicaltrials.gov/>, <http://www.controlledtrials.com/> and <http://www.actr.org.au/>.

Data collection and analysis

Selection of studies

Two authors (YS and AS) independently reviewed titles and abstracts identified from literature searches for relevant trials and selected possibly relevant studies. We reviewed these studies using the full text and assessed them using the inclusion criteria detailed above.

We had agreed that we would resolve any disagreements by discussion between both of the authors; in the case of consensus not being reached, a third author (ES) would become involved and, if necessary, arbitrate.

Data extraction

We stipulated that two authors (YS and AS) would independently extract data using a suitably adapted version of the data extraction form developed by the Cochrane Anaesthesia Review Group. We stated that we would resolve any disagreements by discussion

between both of the authors; in the case of consensus not being reached, a third author (ES) was to be involved and, if necessary, arbitrate. This did not prove necessary.

Assessment of methodological quality of included studies

In our previous version we planned to grade each parameter of trial quality as: A - low risk of bias; B - moderate risk of bias; C - high risk of bias. We planned to make an overall assessment for each randomized controlled trial, using the same rating scale.

In this updated version of the review we planned to assess the quality of included RCTs following the Cochrane approach using the methods detailed in Chapter Eight of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2009).

We planned to construct risk of bias tables to support judgements of quality using the Cochrane Risk of Bias tool (Higgins 2009):

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated interventions adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a risk of bias?

We planned to record the judgement as 'yes' indicating that the study met that quality parameter, 'no' it did not or 'unclear' indicating that there was insufficient evidence to make a judgement either way.

We planned to display the results by creating a 'Risk of bias' graph and a 'Risk of bias' summary figure using RevMan 5.0 software

We also planned to subject quasi-randomized studies to methodological assessment, in which case two authors (YS and AS) would independently assess study quality; review authors would not be masked to study details. We planned to assess the agreement of review authors on methodological quality assessment and to resolve disagreements by discussion and, if necessary, with the involvement of a third author (ES).

Data analysis

We proposed to use Review Manager (RevMan 5.0) for data analysis and quantitative data synthesis. For dichotomous data, we planned to calculate individual and pooled statistics as relative risks (RR) with 95% confidence intervals (95% CI). For continuous

data, we planned to calculate individual and pooled statistics as mean differences (MD) or standardized means differences, or both, with 95% CI. We planned to consider the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. We assumed significant heterogeneity if the I^2 statistic was greater than 40% (that is more than 40% of the variability in outcome between trials could not be explained by sampling variation) (Higgins 2002). We planned to undertake meta-analysis using a fixed-effect model in the absence of statistical heterogeneity and a random-effects model if such heterogeneity was likely. We planned to explore any statistical or clinical heterogeneity by using sensitivity or subgroup analysis (see below). We planned to undertake quantitative analyses of outcomes on an intention-to-treat basis, wherever possible. We planned to assess any evidence of publication bias graphically using funnel plots and statistically using Begg and Egger tests (Begg 1994; Egger 1997).

Subgroup analysis

In the event of uncovering significant heterogeneity, we planned to investigate the heterogeneity by undertaking subgroup analyses. Our subgroups of interest were:

- presence or absence of shock;
- mild or more severe anaphylaxis (Brown 2004b);
- mode of administration of treatment (i.m. versus i.v.; administered by patient versus healthcare professional);
- time from onset of anaphylaxis to receiving treatment;
- age (infants, children, and adults);
- trigger agents (iatrogenic versus community, antibiotic versus other drugs, and muscle relaxants versus other agents).

Sensitivity analysis

We planned to undertake sensitivity analysis for the allocation of missing data by best and worst case analysis and also to undertake sensitivity analysis on the basis of only including randomized studies. This would allow an assessment of the impact on the review conclusions of excluding quasi-randomized studies, judged to be at increased risk of bias.

RESULTS

Description of studies

In the previous version of our review, we searched the databases until March 2007 and yielded 382 citations. In this updated version we searched from March 2007 up to November 2010 and found an additional 1036 citations. In total our combined searches found 1418 citations (see Figure 1).

Figure 1. Search flow diagram

After scrutiny of the abstracts of these studies, no studies fulfilled the inclusion criteria. We contacted context editors and pharmaceutical companies but this failed to contribute any relevant published or unpublished studies. The search of the UK National Research Register, Current Controlled Trials, and Clinical Trials using anaphylaxis as a keyword identified no useful articles.

Risk of bias in included studies

There were no eligible studies.

Effects of interventions

There were no eligible studies.

DISCUSSION

This review failed to uncover any evidence from prospective, randomized or quasi-randomized trials on the effectiveness of adrenaline for the emergency management of anaphylaxis. Given the relative infrequency of the condition, the speed of onset, the often unexpected occurrence, and the established place of adrenaline in treatment guidelines internationally ([Alrasbi 2007](#)) this lack of evidence for a treatment that was introduced well before the evidence-based medicine era is perhaps unsurprising ([Simons 2007b](#)).

The optimal route of administration and the optimal dose of adrenaline have not yet been defined. In children, it has been shown that subcutaneous administration of adrenaline was associated with a striking difference in the time of

maximum plasma adrenaline concentrations compared with the intramuscular route (Simons 1998). Other studies showed that the average maximum plasma concentration was also significantly higher for the intramuscular route than for the subcutaneous route of administration (Simons 2001). Moreover, guidelines regarding the treatment of anaphylaxis have recommended against use of the subcutaneous route (Chamberlain 1999).

Some disagreement exists about the recommended dose of adrenaline. Almost all of the literature agrees on 0.01 mg/kg in infants and children. Although North American, Australasian, and current UK guidelines suggest a maximum initial dose of 0.3 to 0.5 mg of adrenaline in adults, some older European literature suggests 0.5 to 1.0 mg as a maximum initial intramuscular dose in adults (Alrasbi 2007; Soar 2008).

Delayed injection of adrenaline in anaphylaxis is reported to be associated with mortality (Bock 2001; Bock 2007; Pumphrey 2000; Pumphrey 2007; Greenberger 2007). Given that current evidence supports the relative safety of intramuscular adrenaline, and early administration is believed to be associated with an improved survival, any patient with a serious allergic reaction that is rapid in onset should be a candidate for adrenaline by auto-injector.

Adrenaline has been associated with the induction of fatal cardiac arrhythmias and myocardial infarction. Major adverse events usually occur when adrenaline has been given in an excessive dose, an inadequately diluted intravenous dose, or an overly rapid rate of infusion (Brown 1998; Fischer 1995; Montanaro 2002; Pumphrey 2000). Historically, those individuals thought to be particularly at risk of adverse effects of adrenaline include elderly patients and patients with hypertension, arteriopathies, or known ischaemic heart disease (Bock 2001; Bock 2007; Greenberger 2007; Muller 2007; Pumphrey 2000; Pumphrey 2007; Sampson 1992); however, these patients may also be at increased risk from the anaphylactic episode itself. It is difficult, particularly in retrospect, to dissect potential adverse effects of adrenaline from the known effects of anaphylaxis (Brown 1998; Marone 2004; Pumphrey 2000). Because of potential harm from the use of intravenous adrenaline in inexperienced hands, guidelines generally recommend that the intravenous route is reserved for cases that do not respond to initial treatment with intramuscular adrenaline and where cardiovascular collapse and cardiac arrest is considered imminent. A controlled infusion is safer than bolus administration (Soar 2008). It should be given in a resuscitation area that has electrocardiography and physiological monitoring by medical and nursing staff who are trained in its use (Johnston 2003).

In the past, adrenaline has been available worldwide in metered-dose inhaler formulations. These are no longer available in many countries due to their chlorofluorocarbon (CFC) propellant content and the phase out of CFC-containing medications. Inhalation of a few puffs of adrenaline from a pressurized metered-dose inhaler is not adequate for treatment of most of the symptoms in anaphylaxis. In order to achieve systemic effects, adults need to inhale 20 to 30 puffs, and children need to inhale 10 to 20 puffs (Heilborn 1986; Simons 2000). For an overview of the context in which adrenaline should be used in anaphylaxis: provide supplemental oxygen; place patient in the supine position, if tolerated; start volume resuscitation; and prepare for intubation, the appropriate references should be consulted (Soar 2008).

As there are no controlled trials there is no way to estimate the risk in relation to benefit. Based on the current evidence, we believe that the benefit of using appropriate doses of intramuscular adrenaline is likely to far exceed the risk. Anaesthetists, who see anaphylaxis relatively commonly, usually have sophisticated monitoring in place before, during, and after the event; they report a rapid and predictable response to adrenaline that is near universal. It should be stressed that adrenaline is not contraindicated in individuals with underlying ischaemic heart disease as the decrease in filling pressure due to anaphylaxis is likely to result in further coronary ischaemia (Montanaro 2002). Careful monitoring and avoidance of an adrenaline overdose is necessary in these patients, however.

There is a strong clinical impression that prompt injection of adrenaline is life saving in anaphylaxis. Given the uncertainties surrounding its use, however, a firmer evidence base needs to be developed, if possible. Conducting research in this area is challenging for several reasons, including:

- the established position of adrenaline treatment thereby making it difficult to argue for placebo-controlled trials;
- the ethical issues involved in obtaining informed consent (or deferring consent) in emergency situations (Dec Helsink 1996);
- difficulty in conducting double-blind, placebo-controlled studies due to the transient pharmacologic effects (pallor, tachycardia, tremor) of adrenaline in standard doses that reverse airway obstruction and circulatory collapse;
- logistical issues: anaphylactic episodes usually occur without warning, often in a non-medical setting; differ in severity from one individual to another, and from one episode to another in the same individual;
- difficulty in obtaining baseline measurements;
- the lack of any information on the pharmacokinetics and pharmacodynamics of adrenaline when given to humans during anaphylaxis and a lack of any prospectively collected information on clinical outcomes, both of which are required to construct valid hypotheses and inform sample size calculations for a clinical trial.

AUTHORS' CONCLUSIONS

Implications for practice

We found no relevant evidence for adrenaline use in the treatment of anaphylaxis. We are, therefore, unable to make any new recommendations based on the findings of this review. Guidelines on the management of anaphylaxis need to be more explicit about the basis of their recommendations regarding the use of adrenaline.

Implications for research

Given the routine use of adrenaline in the management of anaphylaxis, there is a need for academic debate about the ethics and practicality of mounting randomized trials in order to define the true extent, if any, of benefits from the administration of adrenaline in anaphylaxis. Specifically, more information is required on the subset of patients more likely to benefit from this therapy and the most appropriate preparations, route, and dose of administration.

Although placebo-controlled trials of adrenaline in anaphylaxis would be unethical, it might be possible to conduct randomized controlled trials comparing two different doses of adrenaline, or two different routes of administration of adrenaline, in addition to other standard-of-care treatments (Simons 2008).

Any future trials would need to consider in particular:

- appropriate sample size with power to detect expected difference;
- careful definition and selection of target patients;
- appropriate comparator therapy;
- appropriate outcome measures;
- careful elucidation of any adverse effects; and
- the cost-effectiveness of the therapy.

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As part of the pre-publication editorial process, this review has been commented on by an editor and three peer reviewers (who are external to the editorial team), one or more members of the Cochrane Consumer Network's international panel of consumers and the Anaesthesia Group's Trials Search Co-ordinator.

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APPENDICES

Appendix 1. Search strategy for CENTRAL, The Cochrane Library

```
#1 MeSH descriptor Anaphylaxis explode all trees
#2 anaphylact* near (react* or shock* or syndrom*)
#3 acute near (allergic react*)
#4 anaphylaxis
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Sympathomimetics explode all trees
#7 MeSH descriptor Catecholamines explode all trees
#8 MeSH descriptor Epinephrine explode all trees
#9 MeSH descriptor Norepinephrine explode all trees
#10 sympathomimetic* or Catecholamin* or Adrenalin* or Epinephrin* or Noradrenalin* or EpiPen or Anapen*
#11 (#6 OR #7 OR #8 OR #9 OR #10)
#12 (#5 AND #11)
```

Appendix 2. Search strategy for MEDLINE (Ovid SP)

```
1. exp Anaphylaxis/ or (anaphyla* adj3 (react* or shock* or syndrome* or systemic or idiopathic)).mp. or (acute adj3 allergic react*).mp.
```

2. exp sympathomimetics/ or Catecholamines/ or Adrenaline/ or Epinephrine/ or Noradrenaline/ or (epipen or anapen or catecholamine* or epinephrin* or noradrenalin* or adrenalin*).mp.
3. 1 and 2
4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 3. Search strategy for EMBASE (Ovid SP)

1. exp anaphylaxis/ or exp anaphylactic shock/ or (anaphyla* adj3 (react* or shock* or syndrome* or systemic or idiopathic)).mp. or (acute adj3 allergic react*).mp.
2. exp adrenergic receptor stimulating agent/ or exp catecholamine/ or exp catecholamine/ or noradrenalin/ or (epipen or anapen or catecholamine* or epinephrin* or noradrenalin* or adrenalin*).mp.
3. 1 and 2
4. (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or factorial* or placebo* or volunteer* or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 4. Search strategy for CINAHL (EBSCO host)

- S1 (MM "Anaphylaxis")
- S2 TX anaphylax* or anaphilact*
- S3 S1 or S2
- S4 (MH "Sympathomimetics+")
- S5 (MH "Catecholamines+")
- S6 (MH "Epinephrine")
- S7 TX sympathomimetic* or Catecholamin* or Adrenalin* or Epinephrin* or Noradrenalin* or EpiPen or Anapen*
- S8 S4 or S5 or S6 or S7
- S9 S3 and S8

Appendix 5. Search strategy for BIOSIS Previews (Ovid SP)

- 1 (anaphylact* or anaphylax* or (acute adj3 allergic)).mp.
- 2 (epipen or anapen or catecholamine* or epinephrin* or noradrenalin* or adrenalin*).mp.
- 3 1 and 2

Appendix 6. Search strategy for ISI Web of Science

(TS=anaphylax* OR TS=anaphylact*) AND (TS=Sympathomimetic* OR TS=Catecholamin* OR TS=Adrenalin* OR TS=Epinephrin* OR TS=Noradrenalin* OR TS=EpiPen OR TS=Anapen)

Appendix 7. Search strategy for LILACS (BIREME)

("epipen" or "anapen" or "catecholamine" or "epinephrine" or "noradrenaline" or "adrenaline") and ("ANAPHYLAXIA" or "ANAPHYLAXIS" or "ANAPHYLAXIS/" or "ANAPHYLACTIC REACTION" or "ANAPHYLACTIC REACTION/" or "anaphylax\$" or "anaphylact\$")

Appendix 8. List of experts and pharmaceutical companies contacted

Contact names
Prof. H.A. Sampson
Prof. A.F. Brown
Prof. J.M. Negro-Alvarez
Prof. A.D. Moneret - Vautrin
Prof. U Muller

(Continued)

Prof. M Fisher

Prof. J Ring

Dr. L.P. Lieberman

Dr. P.W. Ewan

Dr. R.S. Pumphrey

Dr. A. Helbling

Dr. R Lin

Dr. S Clark

Dr. D Golden

Dr. R Lockey

Dr. A Bock

Dr. S Kemp

Dr. C Camargo

ALK-Abelló (UK) Ltd

Abbott Laboratories Ltd

UCB Pharma Ltd

Meridian Medical Technology Inc

Cell Therapeutics (UK) Ltd

CSL Biotherapies

Lincoln Medical Ltd

Dey Laboratories

International Medication Systems (UK) Ltd

WHAT'S NEW

Date	Event	Description
14 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care
18 June 2014	Review declared as stable	This Cochrane review has been marked as stable no longer being updated as there are no randomized controlled trials (RCTs) and

Date	Event	Description
		for ethical reasons there are unlikely to be any RCTs in the future. If the situation changes then the authors will update the review.

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 4, 2008

Date	Event	Description
29 January 2016	Amended	New contact details for lead author
23 February 2012	Amended	Contact details updated.
18 January 2012	Amended	Contact details updated.
15 December 2010	Amended	New declaration of interest statement. Previously all authors stated: 'none known'.
30 November 2010	New search has been performed	In the previous version of our review, we searched the databases until March 2007. In this updated version we reran the database searches until November 2010. We did not find any new studies which fitted our inclusion criteria. We updated the methods section.
17 March 2010	Amended	Aziz Sheikh's affiliation updated; typos corrected.
11 December 2007	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Aziz Sheikh (AS) and F. Estelle R Simons (ES)

Co-ordinating the review: AS

Undertaking manual searches: Yasser A Shehata (YS)

Screening search results: YS and AS

Organizing retrieval of papers: YS

Screening retrieved papers against inclusion criteria: YS and AS

Appraising quality of papers: Not applicable

Abstracting data from papers: Not applicable

Writing to authors of papers for additional information: YS and AS

Providing additional data about papers: Not applicable

Obtaining and screening data on unpublished studies: Not applicable

Data management for the review: YS

Entering data into Review Manager ([RevMan 5.0](#)): YS

RevMan statistical data: Not applicable

Other statistical analysis not using RevMan: Not applicable

Double entry of data: (data entered by person one: data entered by person two:) Not applicable

Interpretation of data: Not applicable

Statistical analysis: Not applicable

Writing the review: AS, ES, Simon GA Brown (SB) and YS

Securing funding for the review: AS

Performing previous work that was the foundation of the present study: AS, ES and SB

Guarantor for the review (one author): AS

Person responsible for reading and checking review before submission: AS

DECLARATIONS OF INTEREST

Aziz Sheikh: has obtained funding from ALK-Abello to support conference attendance by members of our research group.

Yasser A Shehata, Simon GA Brown and F Estelle R Simons: none known.

SOURCES OF SUPPORT

Internal sources

- University of Edinburgh, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic Agonists [*therapeutic use]; Anaphylaxis [complications] [*drug therapy]; Epinephrine [*therapeutic use]; Shock [complications] [*drug therapy]; Vasoconstrictor Agents [therapeutic use]

MeSH check words

Humans