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Corticosteroids in management of anaphylaxis; a systematic review of evidence

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Abbreviations

ED, Emergency department; IgE, Immunoglobulin E; IL-6, Interleukin 6; IL-33, Interleukin 33; PAF, Platelet activating factor; RCT, Randomized control trial; TNF α , Tumor necrosis factor α .

Introduction

Anaphylaxis is a “serious, generalized or systemic acute immunologic reaction” that is “rapid in onset and that would be fatal or life threatening” (1-3). Based on available data from international studies, the life-time prevalence of anaphylaxis has been estimated at 0.05 to 2% (4), with an estimated incidence ranging from 10 to 20/100,000 population per year (5-7). The incidence of anaphylaxis is also reportedly increasing worldwide, particularly food-induced anaphylaxis (8,9).

Summary

As anaphylaxis is a medical emergency, there are no randomized controlled clinical trials on its emergency management. Therefore, current guidelines are mostly based on data from observational studies, animal and laboratory studies. Although epinephrine is the mainstay of recommended treatment, corticosteroids are also frequently used. This review evaluates the evidence on the use of corticosteroids in emergency management of anaphylaxis from published human and animal or laboratories studies. Thirty original research papers were found with 22 human studies and eight animal or laboratory studies. The average rate of corticosteroid use in emergency treatment was 67.99% (range 48% to 100%). Corticosteroids appear to reduce the length of hospital stay, but did not reduce revisits to the emergency department. There was no consensus on whether corticosteroids reduce biphasic anaphylactic reactions. None of the human studies had sufficient data to compare the response to treatment in different treatment groups (i.e. corticosteroids, epinephrine, antihistamines). Animal studies demonstrated that corticosteroids act through multiple mechanisms. These modulate gene expression, with effects becoming evident 4 to 24 hours after administration. A much quicker response has been detected within 5 to 30 minutes, through blockade of signal activation of glucocorticoid receptors independent of their genomic effects. Therefore, we conclude that there is no compelling evidence to support or oppose the use of corticosteroid in emergency treatment of anaphylaxis. However, based on the available data, it appears to be beneficial and there was no evidence of adverse outcomes related to the use of corticosteroids in emergency treatment of anaphylaxis.

Anaphylaxis is brought about by direct or indirect activation of mast cells. Anaphylaxis classically involves the skin (80%), respiratory (70%), gastrointestinal (30-45%), cardiovascular (10-45%) and central nervous (10-15%) systems (2,6,10-12). Symptoms generally appear suddenly, progress over minutes to hours and increase in severity. Although only one organ system may be initially involved, symptoms will typically progress to eventually involve at least two organ systems (13,14). The diagnosis of anaphylaxis relies heavily on clinical judgment due to

the lack of availability of rapid diagnostic tests (13,15). Therefore, given the heterogeneity of presentation, there are widespread concerns regarding under diagnosis, under reporting and inadequate treatment of anaphylaxis and non-adherence to management guidelines (16-18).

As anaphylaxis is a medical emergency, conducting randomised control trials (RCT) on treatment of anaphylaxis is practically and ethically problematic. A Cochrane review published in 2013 concluded that there is no evidence from high quality studies for the use of steroids in the emergency management of anaphylaxis (19). The evidence base underpinning the currently recommended first-line of treatment epinephrine is also based on observational studies and extrapolated from laboratory studies. Although not as robust as evidence from RCTs, a systematic analysis of published data on other treatment modalities in the emergency management of anaphylaxis could lead to beneficial inferences.

Pathogenesis of anaphylaxis

The underlying pathogenesis of classical anaphylaxis involves IgE, synthesized in response to exposure to an allergen, becoming fixed to a high affinity receptors for IgE (FcεRI receptors) on the surface membranes of mast cells and basophils (11). On re-exposure to the same allergen, receptor-bound IgE molecules aggregate and results in cell activation. Activation of multiple tyrosine kinases (i.e. Lyn, Syk, and Fyn) with both positive and negative regulatory responses on the signal transduction cascade (20) leads to calcium influx in to the cells leading to cell degranulation (21,22). Mast cells and basophils release preformed chemical mediators and those that are synthesized de novo. Preformed mediators include histamine, tryptase, carboxypeptidase A, and proteoglycans. Inflammatory cytokines, such as IL-6, IL-33 (21,22) and TNF-α, a late-phase mediator are also released from mast cells as preformed mediators. Downstream activation of phospholipase A2 (PLA2), cyclooxygenases and lipoxygenases, leads to the production of arachidonic acid metabolites such as leukotrienes, prostaglandins and platelet activating factor (PAF). Furthermore, IgE enhances expression of FcεRI receptors on mast cells and basophils and increases the intensity of anaphylaxis.

In addition to this, non-IgE mediated mechanisms have also been implicated in anaphylaxis. IgG mediated anaphylaxis has been reported due to triggers such as high molecular weight iron dextran, infusion of chimeric and therapeutic monoclonal antibodies such as infliximab (23,24). Hemodialysis, liposomal drugs, polyethylene glycols and heparin contaminated with over sulfated chondroitin sulfate have been reported to cause complement-mediated anaphylaxis by generation of kallikrein, bradykinin, and complement protein-derived anaphylatoxins C3a and C5a (25). Factor XII and the coagulation system are also

postulated to be involved. There could also be a direct activation of the innate immune system triggering anaphylaxis as in peanut allergies (26). Idiopathic anaphylaxis has been described in some individuals in whom FcεRI receptors may aggregate through autoimmune mechanisms (27). The mechanism by which certain triggers such as exercise, cold air or water exposure and radiation induce anaphylaxis is not yet fully understood. Irrespective of the initiating mechanism, mast cells and basophils play a central role in mediating an anaphylactic reaction. The release of cellular mediators leads to end-organ responses in the skin, respiratory tract, cardio-vascular system, gastrointestinal tract and perhaps the nervous system (14). Most anaphylactic reactions are uniphasic. However, additional patterns of reactions have been described i.e. delayed onset, biphasic reactions and protracted or persistent reactions (28). In biphasic reactions, the initial reaction is followed by a relatively symptom-free period and the symptoms recur, often in a more severe and refractory to therapy form (29). The exact mechanism involved in each of these patterns is not yet fully understood.

Guidelines on treatment of anaphylaxis

Currently, the recommended mainstay of therapy in the event of an anaphylaxis is epinephrine given either intramuscularly or intravenously in specialist settings (14,30-33). It counters most of the pathophysiological processes giving rise to anaphylaxis (11,34). Second-line treatments include corticosteroids, H1- and H2-antihistamines, and bronchodilators. Unlike with epinephrine, there are differing recommendations regarding the use of glucocorticoids and other additional therapies in emergency management of anaphylaxis (35). Recommended emergency treatment of anaphylaxis according to recent guidelines is summarized in **table 1**.

The American (13) guidelines state that there is no place for glucocorticoids in emergency management of anaphylaxis. The British (36), European (30), Australasian (33), Canadian (37) and the World Allergy Organisation (31) guidelines recommend glucocorticoids as a second-line / adjuvant therapy after initial treatment with adrenaline and acknowledge the lack of robust evidence to support this practice (13,30,31,38). The recommended type, route, dose and duration of therapy of glucocorticoids are also varied. Prednisolone, methylprednisolone, dexamethasone and hydrocortisone administered orally, intravenously or intramuscularly are advocated in different guidelines (35). These are given as a single dose or continued for few days as a short course after the initial event (2,35,39).

Mechanism of action of glucocorticoids in anaphylaxis

The use of glucocorticoids in anaphylaxis is supported by the logical deduction of how the mechanism of action of glucocor-

Table 1 - Summary guidelines on emergency management of anaphylaxis.

Organisation, country, year of publication, reference	First line of therapy, route	Glucocorticoids				Other therapies
		Recommendation	Type	Route, dose	Dose	
World Allergy Organization, 2015	Adrenaline, IM	To prevent biphasic reactions. No effect on initial symptoms	Not given	Not given	Not given	Second or third-line: H1 antihistamines, H2-antihistamines
Australasian Society of Clinical Immunology and Allergy (ASCIA), Australia, 2015	Adrenaline, IM	Adjuvant	Prednisolone	Oral	1 mg/kg, maximum 50 mg daily	Glucagon, metaraminol, vasopressin
European Academy of Allergy and Clinical Immunology, 2014	Adrenaline, IM	Third-line	Not given Budesonide	Systemic, Nebulized	Not given Not given	Second-line: inhaled short-acting beta-2 agonists; Third-line: Oral H1- (and H2)-antihistamines
American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI), USA, 2014	Adrenaline, IM	Adjuvant, not effective in the acute management of anaphylaxis	Methylprednisolone	Intravenous	1 to 2 mg/kg	glucagon, b-agonist, H1 and/or H2 antihistamines
			Prednisone	Oral	1 mg/kg, up to 50 mg	
Canadian Paediatric Society, Canada, 2010	Adrenaline, IM	Second-line	Prednisone	Oral	1 mg/kg PO (maximum 75 mg)	second-line agents: cetirizine, diphenhydramine, ranitidine, salbutamol, glucagon
			Methylprednisolone	Intravenously	1 mg/kg IV (maximum 125 mg)	
Working Group of the Resuscitation Council, UK, 2008	Adrenaline, IM	Second-line	Hydrocortisone	Slow intravenous or intramuscular	200 mg	Adjuvant therapies: salbutamol (inhaled or IV), ipratropium (inhaled), aminophylline (IV) or magnesium (IV). When initial resuscitation with adrenaline and fluids has not been successful: noradrenaline, vasopressin, metaraminol and glucagon

ticoids counteracts the pathophysiological processes in anaphylaxis. It is also drawn from evidence of their efficacy in treatment of diseases mediated by similar immunological responses such as asthma (40,41). An illustration of the mechanism of glucocorticoids in anaphylaxis is given in **figure 1**.

Glucocorticoids are potent inhibitors of inflammatory processes and potent anti-allergic compounds reducing the number, maturation and activation of mast cell, which play a central role in anaphylaxis (42-44). They act through modulation of gene expression, and therefore require 4 to 6 hours for the effects to manifest (45). These anti-inflammatory effects are mediated by direct binding of the glucocorticoid / glucocorticoid receptor complex to specific elements in the promoter region of genes, or by interacting with other transcription factors such as the activating protein-1 or nuclear factor-kappa B (40,41,46). For example, in the mast cells, glucocorticoids down-regulate transcription of pro-inflammatory molecules such as cytokines,

chemokines, arachidonic acid metabolites and directly regulate multiple signaling and adaptor molecules (47). These genomic effects of glucocorticoids are relatively delayed with the maximal effect being detected at 2 hours (48). Thus, seemingly little evidence supports their use in emergency management of anaphylaxis, as many aspects of glucocorticoids action were initially thought to be both time and transcription-dependent.

However, recent studies have shown that glucocorticoids also exert rapid non-genomic effects, which can be non-specific or specific (10,49,50), brought about by membrane interactions at high concentration (51) or mediated by interactions with intracellular receptors or membrane-bound receptors (52,53). In some cases, these are thought to be mediated through the classical steroid receptor that functions as a ligand-activated transcription factor. Two animal studies have shown that glucocorticoids have detectable inhibitory effects on anaphylaxis within 5 to 30 minutes, mostly through blockade of these glucocorticoid

Figure 1 - Pathogenesis of anaphylaxis and mechanism of action of glucocorticoids.

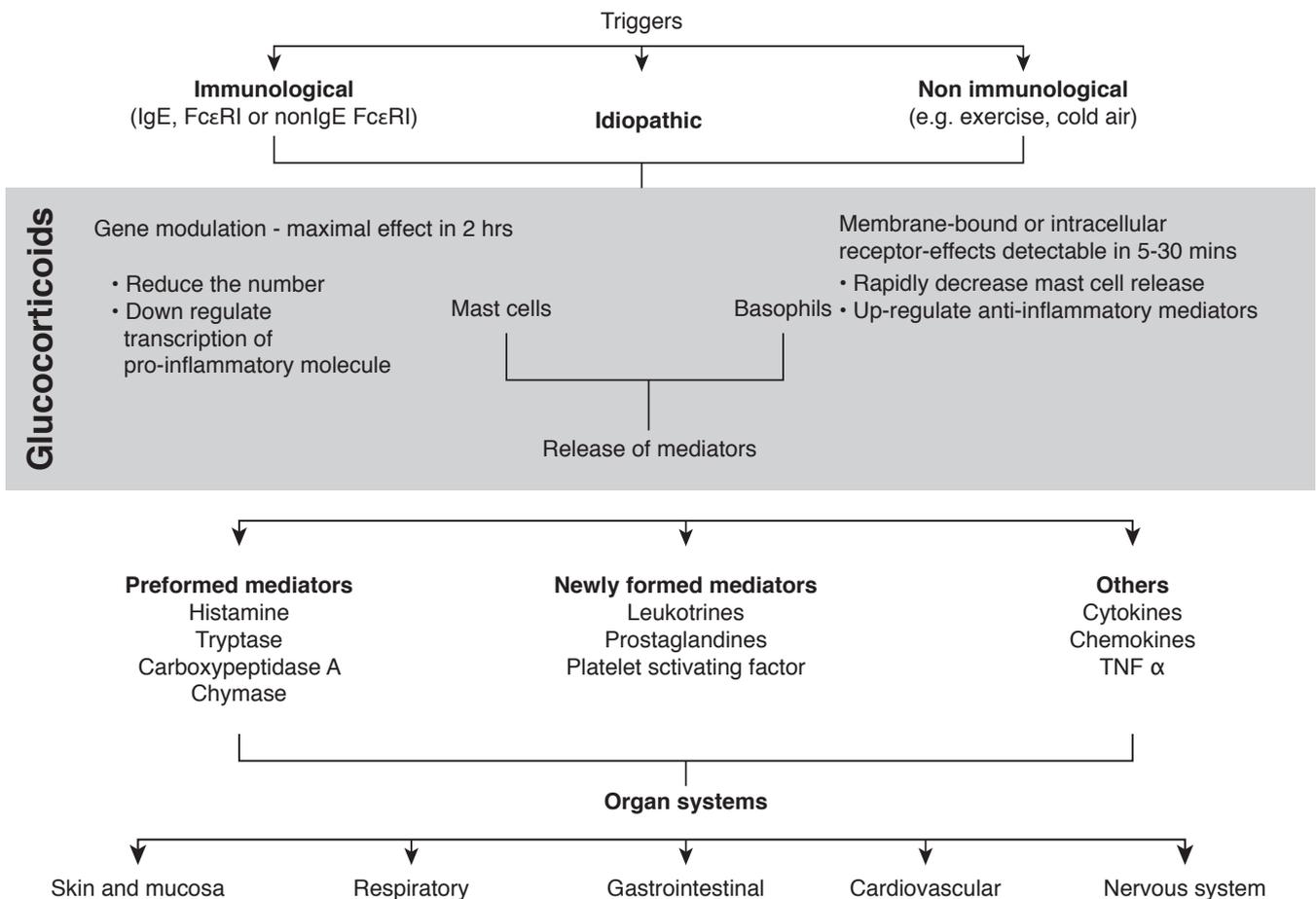
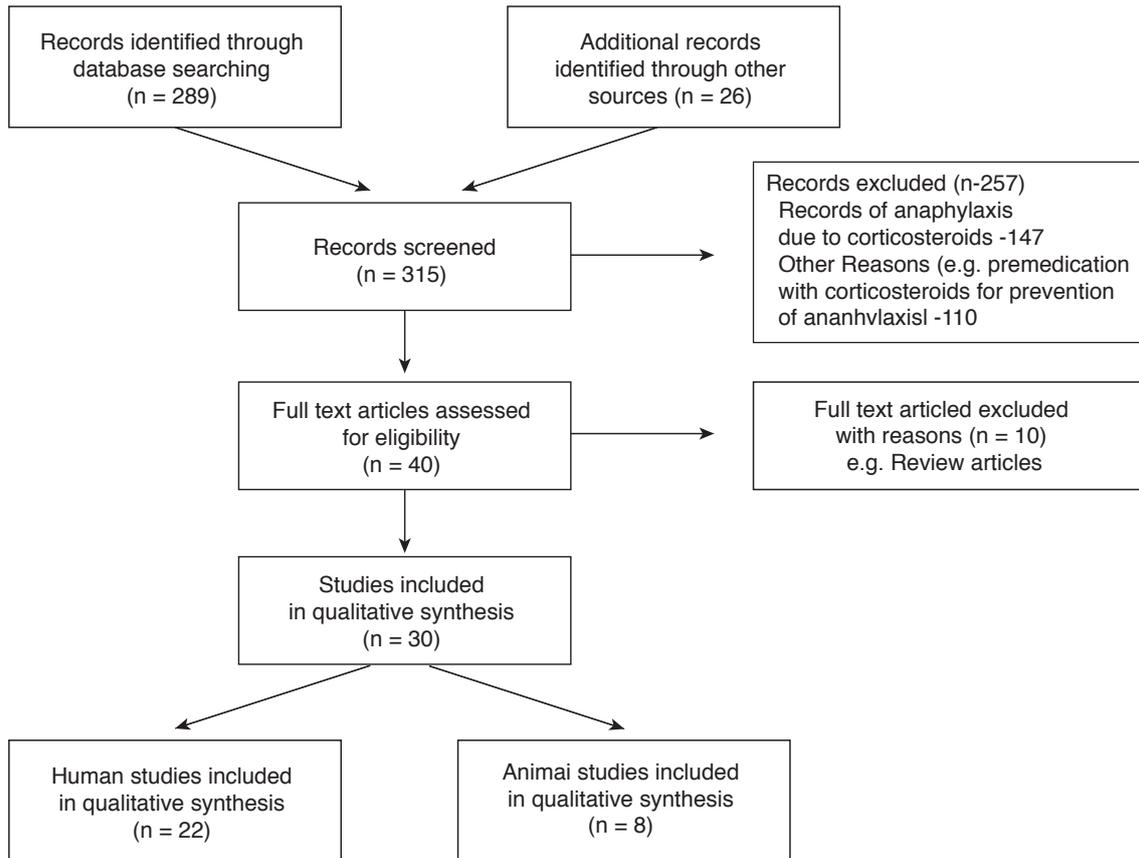


Figure 2 - Summary of search strategy and results.

receptors (52,53). There are diverse rapid effects of glucocorticoids, ranging from activation of adenylyl cyclase, mitogen-activated protein kinases (MAPKs), guanosine triphosphate-binding proteins, and protein kinase C (54). Glucocorticoids rapidly decrease histamine release from the mast cell surface and up-regulate anti-inflammatory mediators (46,49,55).

The lack of concrete evidence and the ethical and practical difficulties in conducting randomised control trials on acute management anaphylaxis is challenging for researchers and clinicians alike. This paper aims to review and systematically document the evidence on the use of corticosteroids in emergency treatment of anaphylaxis and identifies clinical research priorities.

Search strategy

Searched libraries included Pubmed / Medline from inception to March 2016. Additional references were found through cross-references from articles and reviews. The key words used included anaphylaxis, allergy, hypersensitivity, corticosteroids, glucocorticoids, steroids, dexamethasone, hydrocortisone, pred-

nisolone. Human and animal studies on glucocorticoids for management of allergy or anaphylaxis in peer-review journals were included. The search was refined by language (English).

Results

The original search found 289 articles in PubMed (**figure 2**). Twenty-six additional articles were identified through other sources. However, 147 of these were found to be on anaphylaxis due to corticosteroids. There were 28 relevant original research papers reviewed with 22 human studies and 8 animal or laboratory studies. The human studies included 19 retrospective cohort studies, one cross sectional descriptive study and two prospective cohort studies.

Use of corticosteroids in anaphylaxis: human studies

The relevant papers on human studies are summarised in **table 2**. The rate of corticosteroid use in emergency treatment of anaphylaxis varied from 48% to 100% with an average of 67.99%.

Biphasic anaphylactic reactions were reported in approximately 2.2% to 8.7% of patients reporting to emergency departments (56,57). A study conducted in a tertiary care hospital in Canada has found that those who develop biphasic reactions are less likely to have received epinephrine or corticosteroids during emergency management (58). However, three other studies have not found a significant difference in emergency treatment

with either epinephrine or steroids in those with or without biphasic reactions (56,59). There is some evidence suggesting that the length of hospital stay tends to be shorter in those treated with corticosteroids for anaphylaxis (60). However, it has not been found to reduce the revisits to the emergency department with anaphylaxis or other unrelated causes (61). None of the human studies had sufficient data to comment on the response

Table 2 - Use of corticosteroids in anaphylaxis; human studies.

Author, country, year	Study group	Study type	Percentage treated with steroids	Study objective	Findings relevant to corticosteroids	Study weakness
Jiang et al., China, 2016	1,952 cases of anaphylaxis reported in 907	Retrospective cohort study	72	Epidemiology, clinical features, possible triggers, treatment practices	Mild / moderate and severe reactions equally received corticosteroids (P = 0.118)	There was no comparison of the outcome of different treatment modalities
Michelson KA et al., USA, 2015	5203 patients (aged 1 month to 18 years) presenting to emergency departments at 35 hospitals	Retrospective cohort study	75.9	Association between glucocorticoid treatment and length of hospital stay and parenteral epinephrine beyond the first hospital day	Children receiving glucocorticoids were less likely to have prolonged length of hospital stay Glucocorticoid administration was associated with lower odds of epinephrine administration beyond the first hospital day Glucocorticoid use was not associated with less revisits to the emergency department	
Grunau BE et al., Canada, 2015	2701 patient with a discharge diagnosis code of "allergic reaction". Patients younger than 17 years of age have been excluded	Retrospective cohort study	48	Number of subsequent allergy-related ED visits within 7 days, all cause mortality, the number of clinically important biphasic reactions	Steroid administration does not prevent emergency department recidivism within 7 days	Data from only 2 urban centers has been included
Ko BS et al., Korea, 2015	655 patients with anaphylaxis admitted to the emergency department of a tertiary teaching hospital	Retrospective cohort study	100	Epidemiology, management, disposition, and clinical out-comes	Overall 87.2% were treated with methylprednisolone and 12.8% were treated with hydrocortisone Biphasic reaction occurred in 2.2% of the patients treated with steroids	Patients who have not been treated with steroids have been excluded from the study.

Author, country, year	Study group	Study type	Percentage treated with steroids	Study objective	Findings relevant to corticosteroids	Study weakness
Asia Y et al., Canada, 2014	37,730 patients with anaphylaxis visiting the emergency department of a tertiary care center	Retrospective cohort study	68.1	Demographic characteristics, suspected triggers and management of anaphylaxis	Higher percentage of severe reactions (71.4%) are treated with steroids compared to mild (50.0%) and moderate (67.8%) reactions.	The outcome of treatment is not assessed
Worm et al., Germany, 2014	3333 cases of anaphylaxis over a 3 year period from 10 European countries	Retrospective record analysis of one line data registry	60.4	Epidemiology, symptomatology, triggers, treatment	No additional data provided on steroid use or outcomes	There was no comparison of the outcome of different treatment modalities
Manuyakorn W et al., Thailand, 2013	160 children (aged 3 months to 18 years) diagnosed with anaphylaxis	Retrospective cohort study	93	Epidemiology, symptomatology, treatment practices	92.3% of patients with uniphasic reactions and 93.3% of patients with biphasic reactions are treated with systemic corticosteroids ($P > 0.05$)	Retrospective records analysis. The outcome of treatment is not stated
Rappo et al. Australia, 2013	34 cases anaphylaxis due to tick bite presenting an emergency department	Retrospective cohort study	97%	Epidemiology, symptomatology, course of illness, treatment	71% were discharged on oral prednisolone. One (4.1%) of them developed a biphasic reaction	Retrospective medical record review with a small sample size. There is no comparison of the outcome among the treatment groups
Vezir et al., Turkey, 2013	96 patients presenting to ED	Prospective cohort study	80.2	Epidemiology, symptomatology, triggers, treatment	Only 44.4% received epinephrine	
Hompes S. et al., Germany, 2011	1281 anaphylactic reactions voluntarily reported through an online registry	Cross sectional descriptive study	85	Demography, symptomatology, course of anaphylaxis, treatment	Corticosteroids were given intravenously in 50%, orally in 29%, and through rectal application in 6%.	
Hoffer et al., Israel, 2011	92 children admitted to a single medical center with the diagnosis of anaphylaxis	Retrospective cohort study	85	Epidemiology, symptomatology, course of illness, laboratory findings, treatment, concurrent illnesses	Only 72% were treated with epinephrine 75% received antihistamines	The outcome of the different treatment is not analyzed
Orhan et al., Turkey, 2011	224 cases of anaphylaxis reported in 137 children	Retrospective cohort study	83.5	Epidemiology, symptomatology, course of illness, treatment practices	Only 32.3% received epinephrine	
Sole et al., Brazil, 2011	634 patients from 15 Latin American countries and Portugal with severe allergic reactions	Cross sectional descriptive study	80.5	Epidemiology, symptomatology, triggers, course of illness, treatment, outcome		There is no comparison of outcome of different treatment

Author, country, year	Study group	Study type	Percentage treated with steroids	Study objective	Findings relevant to corticosteroids	Study weakness
Russell et al., USA, 2010	103 patients with the diagnosis of anaphylaxis visiting the emergency department	Retrospective descriptive study	79	Epidemiology, symptomatology, triggers, course of illness, treatment, outcome	Only 56% received intramuscular epinephrine	
De Swert et al., Belgium, 2008	64 cases of anaphylaxis	Prospective cohort study	45.6	Epidemiology, clinical features, triggers, treatment practices, outcome	Only 9.1% received epinephrine	Small sample size
Ellis AK & Day JH, Canada, 2007	134 patients with anaphylaxis (in-patients and outpatients) at a tertiary care center	Retrospective cohort study		Presence of biphasic reaction, course of illness, treatment	Biphasic reactors received less epinephrine and tended to receive less corticosteroid	
Gaeta et al., USA, 2007	12.4 million allergy-related emergency department visits with 1% being coded as anaphylaxis over a 9 year period	Retrospective cohort study	50	Epidemiology, symptomatology, triggers, treatment	Corticosteroid use increased during the study period (22% to 50%; $P < 0.001$) Epinephrine use was infrequent and declining (19% to 7%; $P = 0.04$)	
Clark et al., USA, 2005	617 with anaphylaxis presenting to the ED with in a one year period	Retrospective cohort study	49	Epidemiology, symptomatology, triggers, treatment	Only 7% were treated with epinephrine	
Clark et al., USA, 2004	A random sample of 678 charts of patients who presented with food allergy	Retrospective cohort study	48	Epidemiology, symptomatology, triggers, treatment	Only 16% were treated with epinephrine	
Brown et., Australia, 2001	162 patients with acute allergic reactions and 142 patients with anaphylaxis	Retrospective cohort study	78	Epidemiology, clinical features, possible triggers, treatment practices, outcome	Only 40% received epinephrine	A retrospective record analysis
Lee JM & Greenes DS, USA, 2000	106 inpatient (108 anaphylaxis episodes)	Retrospective cohort study		Symptomatology, course of illness, treatment	Patients with or without biphasic reactions did not differ significantly in the incidence of initial epinephrine use, initial steroid use	
Stewart & Ewan, 1996	9 patients with anaphylaxis admitted to ED	Retrospective cohort study	77.8	Epidemiology, symptomatology, triggers, treatment practices, outcome		A patient record analysis with a small sample size

to treatment in different treatment groups (i.e. corticosteroids, epinephrine, antihistamines).

Use of corticosteroids in anaphylaxis; animal and laboratory studies

The findings of the relevant papers are summarized in **table 3**. The animal models used included guinea pigs (62-64) and mice (48,53,65,66). One other study was conducted using A549 human adenocarcinoma cell line (52). Most investigated the effect of pretreatment with glucocorticoids. The postulated mechanisms of action include action through modulation of gene expression occurring 4 to 24 hours after treatment with glucocorticoids (48,65) and blockade of signal activation of glucocorticoid receptors independent of its genomic effects (52,53). The latter response has been detectable within 5 to 30 minutes (52,53). Interestingly, prednisolone has been found to inhibit passive cutaneous anaphylaxis in a biphasic manner at 8-12 and 24 hours (48).

Discussion

Anaphylaxis is an acute immunologic reaction due to direct or indirect activation of mast cells. Prompt definitive management can be life saving, and any delays may result in a fatal outcome. Irrespective of the trigger, management of anaphylaxis is the same for all patients. Although epinephrine is clearly recommended as the first line treatment for management of anaphylaxis, human studies reviewed here revealed that usage of epinephrine either during pre-hospital or emergency care varies widely from 7-70% (12). This could be due to over-prudent hesitancy to administer epinephrine with the fear of serious adverse effects. Conversely, there is a lower threshold to initiate glucocorticoid therapy in patients with anaphylaxis. Despite the lack of any strong recommendations, 45-97% of the patients receive glucocorticoids in emergency management of anaphylaxis (16,39,67,68). Some multicenter trials have demonstrated that corticosteroids are still being administered as the first-line therapy instead of epinephrine (17,18,39).

When considering the pathogenesis of anaphylaxis and the mechanism of action of glucocorticoids, it becomes evident that glucocorticoids have a theoretical benefit in treatment of anaphylaxis. For many years, glucocorticoids were thought to act through nuclear receptors by modulating gene expression, hence having delayed onset of action. However, recent advancements have demonstrated that glucocorticoids induce a rapid anti-inflammatory effect by a non-genomic mechanism, acting through membrane-bound or cytosolic receptors. Laboratory studies have demonstrated a detectable response in as little as 5 minutes from the point of administration.

Most cases of anaphylaxis resolved after initial treatment. One to 20% will develop a biphasic reaction, a delayed recurrence of illness occurring hours after improvement of the symptoms (59,61,69). There are multiple factors that have been described to be associated with biphasic reactions including under-treatment and delay in treatment (58,59). The World Allergy Organisation recommends the administration of glucocorticoids to prevent such biphasic reactions, and states that there are no or minimal effects on initial symptoms (31). This is supported by laboratory studies, which demonstrate that prednisolone inhibits passive cutaneous anaphylaxis in a biphasic manner. However, except for one retrospective cohort study, none of the other human studies found that glucocorticoids lower the incidence or prevents the progression of symptoms.

Although observational studies reveal that those with more severe reactions are more likely to be given corticosteroids, there is no conclusive evidence to infer that early administration of corticosteroids prevents progression of symptoms (56,70). Additional benefits such as shortening the length of hospital stay and reducing the need to repeated epinephrine injections have also been attributed to glucocorticoid therapy in anaphylaxis. A major limitation in the human studies included in this review is the lack of data on the outcome of patients by the treatment received in the emergency department to make a meaningful comparison between treatment groups.

Conclusions

Corticosteroids are often used in the management of anaphylaxis and sometimes used as a first-line therapy instead of adrenaline, despite the lack of compelling evidence and guidelines recommending their use only as an adjuvant therapy. There are no randomised or quasi-randomised trials providing support to this practice. Nevertheless, the pathophysiological basis of anaphylaxis and the mechanism of action of glucocorticoids, particularly the recent evidence of the rapid non-genomic effects provide a rational basis for using corticosteroids in the emergency treatment of anaphylaxis. However, there is no concrete evidence to support or oppose the use of corticosteroids in emergency management of anaphylaxis, particularly as short-term use of glucocorticoids is seldom associated with serious adverse effects (71). Therefore, based on the animal / laboratory studies and human studies reviewed, we conclude that use of glucocorticoids along with administration of epinephrine in the emergency management of anaphylaxis is rational and may be beneficial. Although RCT may not being plausible, more evidence is needed on treatment and treatment outcomes through at least prospective cohort studies. These could provide valid data to evaluate the definitive place of glucocorticoids in the emergency management of anaphylaxis.

Table 3 - Use of corticosteroids in anaphylaxis; animal studies.

Author, Country, Year	Animal model	Study objective	Findings
Obiri et al., USA, 2011	PEP +/- mice	Effect of glucocorticoids in PEST-domain-enriched tyrosine phosphatase (PEP) in bone marrow derived mast cells	Glucocorticoid increased PEP expression in mast cells and only partially inhibited anaphylaxis. Glucocorticoid potently inhibited anaphylaxis when combined with the PEP inhibitor
Croxtall et al., 2000	A549 human adenocarcinoma cell line	Assess the rapidity changes induced by dexamethasone and the mechanism of action	Dexamethasone, inhibits the activation of AA release by EGF by a mechanism without the involvement of the suppression of cPLA2 expression. Blockade of signal activation by dexamethasone was detectable within 5 to 10 mins. The dose-dependence of this inhibitory effect of dexamethasone was the same at 5 min and 3 h. The rapid effect of glucocorticoids is mediated by occupation of glucocorticoid receptor
Miura et al., Japan, 1992	Rats with PCA and cutaneous reactions caused by histamine serotonin and leukotriene C4 elicited at the same time	Inhibitory mechanisms of glucocorticoids in immediate hypersensitivity reactions - passive cutaneous anaphylaxis (PCA) mediated by IgE antibodies and cutaneous reactions caused by histamine serotonin and leukotriene C4	Hydrocortisone, prednisolone and dexamethasone, inhibited all these reactions significantly. Hydrocortisone given 1-4 and 12 hours inhibited PCA significantly. Maximum inhibition observed at 2 hours. Maximum inhibitions of histamine, serotonin and LTC4-induced cutaneous reactions observed at 2 hours. Prednisolone inhibited PCA biphasically at 24 and 8-12 hours. Dexamethasone inhibited PCA persistently between 2 to 12 hours and maximally at 4 hours
Rong & Zhao-Gui, Changsha, 1989	Guinea pigs heart	The protective effect of H1 & H2 antagonists, adenosine and hydrocortisone on cardiac anaphylaxis	Hydrocortisone delayed the onset of arrhythmias and significantly reduced the duration of arrhythmias. When histamine receptor antagonists are used with hydrocortisone, a good protective effect can be achieved
Guhlmann et al., Germany, 1989	Guinea pigs suffering from anaphylactic shock		There was a lack of effect of dexamethasone on anaphylactic LTC4 generation in vivo
Inagaki et al., Japan, 1987	Rats injected with <i>Ascaris suum</i> extract serum	Effect of hydrocortisone, prednisolone and dexamethasone on IgE antibody-mediated homologous passive cutaneous anaphylaxis (PCA)	Injection sites were evaluated 30 minutes after injection. Glucocorticoids inhibited the PCA dose-dependently. They also inhibited the skin reactions caused by histamine, serotonin and LTC4 and reduced vascular permeability
King et al., USA, 1984	Outbred Wistar rats	Effect of glucocorticoids on intestinal anaphylaxis in the rat	Manifestations of anaphylaxis were abolished in rats previously treated with corticosteroids 48 and 24 before This was associated with depletion of RMCP-II and of MMC from the intestinal mucosa detectable at 4-24 hours after treatment
Andersson & Brattsand, Sweden, 1982	Guinea-pigs sensitized to two ovalbumin regimens	Effect of budesonide and hydrocortisone on histamine release from anaphylactically-shocked chopped lung fragments	Budesonide pretreatment reduced the capacity of anaphylactically-challenged chopped lung tissue to release histamine

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