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Research Article

The Relationship Between Allergic Reactions and Serum Erythropoietin Levels: A New Biomarker Candidate in Allergic Reactions

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ABSTRACT

Objective: This study aimed to compare serum erythropoietin (EPO) levels in patients admitted to the emergency department with allergic reactions who were clinically diagnosed with urticaria, angioedema, or anaphylaxis, and to evaluate the diagnostic value of EPO as a potential biomarker.

Methods: The study was conducted prospectively in the Emergency Department of Atatürk University between 2013 and 2016. A total of 156 patients diagnosed with urticaria, angioedema, or anaphylaxis were included. Serum EPO levels from blood samples taken at admission were analyzed using the enzyme-linked immunosorbent assay method. Relationships between vital signs, clinical symptoms, and EPO levels were statistically evaluated.

Results: No significant difference in serum EPO levels was observed among the urticaria (41.7%), angioedema (35.9%), and anaphylaxis (24.4%) groups (P = 0.799). However, patients with uvular edema had significantly higher EPO levels (6.5 ± 1.6 vs. 6.0 ± 1.7 mIU/mL; P = 0.027). In the anaphylaxis group, oxygen saturation and blood pressure were significantly lower, whereas pulse rate and respiratory rate were significantly higher.

Conclusion: EPO levels alone are not sufficient for differential diagnosis of acute allergic reactions. However, when assessed alongside specific symptoms, such as uvular edema, EPO may reflect the severity of the inflammatory response and serve as a potential biomarker. Multicenter studies including tissue-level analyses are needed to better understand the role of EPO in allergic inflammation.

Keywords: Anaphylaxis, angioedema, erythropoietin, hypoxia, urticaria

INTRODUCTION

Allergic reactions are common clinical presentations in emergency departments and often require prompt intervention. These reactions typically manifest in three major forms: urticaria, angioedema, and anaphylaxis. Urticaria is characterized by well-demarcated, erythematous, and often pruritic plaques on the skin, usually resolving spontaneously. Angioedema involves swelling of deeper tissues and is frequently observed in periorbital, perioral, or oropharyngeal regions. Anaphylaxis, on the other hand, is a rapidly developing hypersensitivity reaction following allergen exposure, potentially life-threatening and characterized by systemic inflammatory responses that may impair the respiratory, circulatory, or gastrointestinal systems.[1,2]

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Because of the symptomatic overlap among these clinical entities, differential diagnosis often relies solely on patient history and physical examination. However, this approach may lead to diagnostic uncertainty and delays, particularly in cases of mild anaphylaxis, adversely affecting treatment and prognosis.[3] Indeed, a retrospective study reported that only one in four patients who met the diagnostic criteria for anaphylaxis were correctly identified.[4] This underscores the need for objective biomarkers to aid in diagnosis.

Erythropoietin (EPO) is a glycoprotein hormone secreted by the kidneys in response to hypoxia, stimulating the proliferation of erythroid progenitor cells and enhancing erythropoiesis. During hypoxemia, EPO levels may increase by up to 5- to 8-fold, serving as a compensatory mechanism to improve oxygen delivery.[5] Recent experimental and clinical studies, however, have demonstrated that EPO exerts effects beyond hematopoiesis, particularly on inflammatory processes.

EPO may exert anti-inflammatory effects in immune cells such as macrophages and monocytes by suppressing the release of proinflammatory cytokines, including tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), and by inhibiting nuclear factor-κB (NF-κB) activation, thereby exerting immunomodulatory effects.[6,7] Through these mechanisms, EPO has been shown to reduce tissue damage in systemic inflammatory conditions such as sepsis, trauma, and myocardial ischemia.[8] Moreover, elevated EPO levels have been observed in conditions associated with oropharyngeal edema and hypoxia, suggesting a potential role in the inflammatory process.

Nevertheless, the literature on how EPO levels change in acute allergic reactions and whether these changes carry diagnostic significance remains limited. Existing studies have mainly focused on mast cell activation and tryptase levels, often neglecting the potential role of EPO as a biomarker. Given the variable degrees of hypoxia and inflammatory burden across urticaria, angioedema, and anaphylaxis, investigating the potential utility of EPO for differential diagnosis appears warranted.

In this study, we aimed to compare serum EPO levels among patients presenting to the emergency department with clinically diagnosed allergic reactions (urticaria, angioedema, or anaphylaxis) to evaluate its diagnostic utility in distinguishing these conditions. Additionally, we sought to examine the relationship between specific symptom clusters (e.g., uvular edema, dyspnea) and EPO levels to assess the potential contribution of this biomarker to clinical decision-making.

MAIN POINTS

- This study evaluated the association between serum erythropoietin (EPO) levels and allergic reactions in emergency department patients.
- Serum EPO levels did not differ significantly among patients with urticaria, angioedema, or anaphylaxis.
- Patients with uvular edema had significantly higher EPO levels compared with those without uvular edema.
- These findings indicate that EPO may contribute to the pathophysiology of airway involvement in allergic reactions.

Study Design and Population

This prospective study was conducted between June 2013 and January 2016 in the Department of Emergency Medicine at Atatürk University Faculty of Medicine. The study was approved by the Atatürk University Non-Interventional Clinical Research Ethics Committee prior to patient enrollment (decision no: 25, date: 02.05.2013). Subsequently, when the study was decided to be used as a thesis project, a second ethics committee approval was obtained in accordance with institutional regulations. Patients aged 18 years or older who presented to the emergency department with allergic reactions and were clinically diagnosed with urticaria, angioedema, or anaphylaxis were included. Written informed consent was obtained from all participants.

Exclusion criteria

The following patients were excluded:

- Those with known anemia, chronic renal failure, or liver disease
- Patients with a history of chronic obstructive pulmonary disease or asthma
- Patients with bone marrow disorders or active malignancy
- Those with other systemic diseases that could affect EPO levels

Diagnostic criteria and Patient Classification

- Patients were categorized into three groups based on clinical findings:
- Urticaria: Patients with skin lesions only
- Angioedema: Patients with skin and mucosal edema
- Anaphylaxis: Patients meeting the 2014 diagnostic criteria of the World Allergy Organization.[9]

Data Collection

Vital signs (blood pressure, heart rate, oxygen saturation, respiratory rate) and laboratory parameters [White blood cell, neutrophil, lymphocyte, eosinophil, basophil, red blood cell hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, platelet, platelet distribution width, creatinine, and blood urea nitrogen] were recorded for each patient. Suspected allergens and clinical symptoms (such as pruritus, rash, uvular edema, and stridor) were documented using a standardized form.

Biochemical Analysis

Serum EPO levels were measured in blood samples collected on admission. After clotting, the samples were centrifuged and stored at -80 °C. Measurements were performed using the enzyme linked immune sorbent assay (ELISA) method (Human EPO Platinum ELISA Kit, eBioscience, Austria) in accordance with the manufacturer's protocol.

Statistical Analysis

Data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation when normally distributed, or as median (min-max) when non-normally distributed; categorical variables were presented as percentages (%). The Kolmogorov-Smirnov test was used to assess normality. Comparisons among more than two groups were performed using one-way ANOVA for parametric variables and the Kruskal-Wallis test for non-parametric variables. Post-hoc analyses were conducted with the Bonferroni correction. Comparisons between two groups were made using the Independent-samples t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test. Logistic regression was used to identify independent predictors. A *P* value of < 0.05 was considered statistically significant.

RESULTS

A total of 156 patients were included in the study. Of these, 41.7% (n=62) were diagnosed with urticaria, 35.9% (n=56) with angioedema, and 24.4% (n=38) with anaphylaxis. Among the participants, 45.5% (n=71) were male and 54.5% (n=85) were female. The mean age was 40.9 ± 17.1 years, with no significant age difference between genders ($P > 0.05$). Drugs were the most common cause of allergic reactions (38.2%) and were the leading cause in both males (39.4%) and females (37.6%). The distribution of probable allergens by gender is presented in Table 1.

Vital signs were compared among the three clinical groups using one-way ANOVA. Post-hoc Bonferroni analysis revealed that the anaphylaxis group had significantly lower systolic (111.0 ± 30.9 mmHg) and diastolic (67.2 ± 18.2 mmHg) blood pressure compared with both the urticaria and angioedema groups ($P = 0.004$ and $P < 0.001$, respectively). Additionally, the anaphylaxis group exhibited significantly higher heart and respiratory rates (heart rate: 94.8 ± 18.9 bpm; respiratory rate: 18.5 ± 5.0/min) ($P = 0.008$ and $P < 0.001$, respectively). Oxygen saturation was also significantly lower in the anaphylaxis group (93.3 ± 4.0%; $P = 0.003$). Details of vital signs are shown in Table 2.

Serum EPO levels were compared among the groups: urticaria (6.2 ± 1.7 mIU/mL), angioedema (6.2 ± 1.7 mIU/mL), and anaphylaxis (6.4 ± 1.7 mIU/mL), with no significant differences observed ($P = 0.799$). The results are summarized in Table 3.

In subgroup analyses, EPO levels did not differ significantly by drug allergy, food allergy, rash, or pruritus ($P > 0.05$). However, patients with uvular edema had significantly higher EPO levels (6.5 ± 1.6 mIU/mL) than those without edema (6.0 ± 1.7 mIU/mL; $P = 0.027$). The detailed subgroup comparisons are presented in Table 4.

Table 1. Probable Allergens by Gender

Etiology	Male n (%)	Female n (%)
Drugs	28 (39.4)	32 (37.6)
Idiopathic	26 (36.6)	25 (29.4)
Food	7 (9.9)	11 (12.9)
Insect bites	7 (9.9)	4 (4.7)
Cleaning products	1 (1.4)	1 (1.2)
Clothing	0 (0.0)	2 (2.4)
Infection	1 (1.4)	3 (3.5)
Other	0 (0.0)	5 (5.9)
Cold	1 (1.4)	0 (0.0)
Stress	0 (0.0)	2 (2.4)

Table 2. Vital Signs by Clinical Groups

Parameter	Urticaria (n=62)	Angioedema (n=56)	Anaphylaxis (n=38)	*P* value	Total (n=156)
Systolic BP (mmHg)	125.8 ± 18.9	123.7 ± 15.9	111.0 ± 30.9*	**0.004**	121.5 ± 22.2
Diastolic BP (mmHg)	77.8 ± 12.4	77.9 ± 10.9	67.2 ± 18.2*	**< 0.001**	75.3 ± 14.2
Heart rate (bpm)	87.8 ± 12.5	86.0 ± 10.4	94.8 ± 18.9*	**0.008**	88.9 ± 14.0
Oxygen saturation (%)	94.9 ± 2.4	95.1 ± 2.0	93.3 ± 4.0*	**0.003**	94.6 ± 2.8
Respiratory rate (/min)	16.3 ± 2.3	15.9 ± 1.5	18.5 ± 5.0*	**< 0.001**	16.7 ± 3.2

Values are presented as mean ± standard deviation (SD). Comparisons between clinical groups were performed using one-way ANOVA. Post-hoc analysis was conducted using the Bonferroni correction.
*: Statistically significant compared to the urticaria and angioedema group with the anaphylaxis group ($P < 0.05$).

Table 3. Serum Erythropoietin Levels by Clinical Groups

Parameter	Urticaria (n=62)	Angioedema (n=56)	Anaphylaxis (n=38)	*P* value
Erythropoietin (mIU/mL)	6.2 ± 1.7	6.2 ± 1.7	6.4 ± 1.7	0.799

Data are expressed as mean ± SD. Comparisons among groups were performed using one-way ANOVA.

Table 4. Comparison of Erythropoietin Levels in Subgroups

Parameter	Absent (n)	Mean ± SD (absent)	Present (n)	Mean ± SD (present)	*P* value
Drug allergy	96	6.2 ± 1.5	60	6.2 ± 2.0	0.749
Food allergy	139	6.2 ± 1.7	17	6.4 ± 1.5	0.695
Rash	30	5.8 ± 1.3	126	6.3 ± 1.7	0.159
Pruritus	60	6.1 ± 1.6	96	6.3 ± 1.7	0.467
Uvular edema	89	6.0 ± 1.7	67	6.5 ± 1.6	**0.027**

Values are presented as mean ± SD. Comparisons were made using Student's t-test.

DISCUSSION

In this study, serum EPO levels were examined in patients who presented to the emergency department with allergic reactions and were clinically diagnosed with urticaria, angioedema, or anaphylaxis. Our findings showed no significant differences in EPO levels among these three clinical conditions. However, the observation of significantly higher EPO levels in patients with uvular edema is noteworthy. This suggests that EPO may be involved not only in responses to hypoxic stimuli but also in inflammatory processes.

Anaphylaxis is a rapidly developing systemic hypersensitivity reaction that often affects the respiratory or circulatory systems and is life-threatening. During anaphylaxis, mast cells and basophils are activated via FcεRI receptors, leading to the release of histamine, tryptase, prostaglandin D2, and various cytokines. The resulting bronchoconstriction, vascular leakage, and vasodilation cause hypoxia, tachycardia, and hypotension.[9,10] In our study, patients with anaphylaxis exhibited significantly lower oxygen saturation, systolic and diastolic blood pressure, whereas their heart rate and respiratory rate were significantly higher. These findings confirm the presence of hypoxia and hemodynamic compromise.

EPO is a glycoprotein hormone secreted by the kidneys in response to hypoxia; it stimulates erythropoiesis. EPO production typically increases within several hours in response to low tissue oxygen tension. However, some studies have shown that EPO may also play a role in inflammatory processes. By exerting anti-inflammatory effects on macrophages and monocytes, EPO suppresses proinflammatory cytokines such as TNF-α and IL-6 and inhibits NF-κB activation, thereby providing immunomodulation.[6,7] With these properties, EPO has been considered a tissue-protective agent in conditions such as sepsis, myocardial ischemia, and trauma.[8]

Although no overall differences in EPO levels were found among clinical groups, the significantly higher levels observed in patients with uvular edema are noteworthy. The uvula, located in the upper airway, may be exposed to both mechanical and inflammatory stress. An experimental study demonstrated infiltration of cluster of differentiation 4 (CD4) and CD8+ T cells and macrophages into the uvular tissue, contributing to inflammation.[11] Such cellular infiltration may enhance local cytokine release, thereby stimulating EPO production.

The relationship between uvular edema and hypoxia may also trigger systemic EPO release. Reports in the literature indicate that EPO levels can increase five- to eightfold in hypoxic states.[5] However, the timing of this increase is critical. Some studies have indicated that EPO does not rise significantly within hours of acute hypoxia, suggesting that early serum measurements may not fully capture this response.[12] The absence of significant EPO elevation in the anaphylaxis group in our study may, therefore, be related to this physiological delay.

Interestingly, immune responses against EPO itself have been described, leading to allergic reactions. Cases of angioedema, urticaria, and even anaphylaxis associated with recombinant EPO and its derivatives have been reported.[13,14] These findings suggest that EPO may interact bidirectionally with the immune system, functioning both as a stimulus and as a target.

Our findings indicate that EPO levels alone are insufficient for distinguishing among urticaria, angioedema, and anaphylaxis. However, when evaluated alongside specific findings, such as uvular edema, they may have clinical relevance. This suggests the potential role of EPO as an inflammatory biomarker, although further histopathological and immunological studies at the tissue level are warranted.

Finally, it has been suggested that the anti-inflammatory effects of EPO require plasma levels above a certain threshold, which may be higher than the threshold needed for hematopoietic effects.[15] Thus, even if serum levels remain stable during acute inflammation, local tissue-level effects of EPO may persist.

Study Limitations

This study has several methodological and structural limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability of the results. Additionally, molecular parameters, such as erythropoietin receptor (EPOR) expression and tissue-level EPO accumulation, could not be evaluated, leaving the tissue-level correlates of the observed serum differences unknown.

Furthermore, correlations with other inflammatory biomarkers, such as tryptase, histamine, and IL-6, were not examined, nor were mast cell density or IgE levels in urticarial lesions assessed. Finally, the study was conducted at a high-altitude center (1850 m), which may differ from other centers with respect to hypoxic stimuli.

Recommendations:

Large-scale, multicenter studies are recommended to more reliably evaluate the diagnostic value of serum EPO levels in allergic conditions.

Molecular parameters, such as tissue-level EPO expression, EPOR presence, and local cytokine profiles, should be investigated to clarify the role of EPO in allergic inflammation.

Evaluating EPO levels when specific symptoms are present, particularly uvular edema, may help predict clinical severity.

The timing of the EPO response to acute hypoxia should be examined further in detailed time-course studies in the context of allergic reactions.

Developing a biomarker panel incorporating acute-phase reactants such as histamine, tryptase, and IL-6 alongside EPO may improve the accuracy of the diagnosis of anaphylaxis in emergency settings.

CONCLUSION

This study is a pioneering analysis of the diagnostic value of serum EPO levels in patients with acute allergic reactions, such as urticaria, angioedema, and anaphylaxis. Our results revealed no significant differences in EPO levels among these three clinical conditions. However, the significantly higher EPO levels in patients with uvular edema suggest that this finding may serve as an indicator of systemic inflammatory activity.

Overall, EPO levels appear insufficient as a standalone biomarker for the differential diagnosis of allergic reactions. However, when assessed in conjunction with specific symptoms such as uvular edema, EPO may contribute to clinical decision-making. This finding implies that EPO elevation may reflect not only hypoxic responses but also inflammation-related processes.

In this context, uvular edema emerges as a clinically significant sign with dual implications: a risk of local airway obstruction and an indicator of the severity of systemic inflammation. The observed association between uvular edema and increased EPO levels suggests that uvular edema should be considered an active finding requiring careful evaluation in emergency departments, rather than a passive clinical observation.

Ethics

Ethics Committee Approval: The study was approved by the Atatürk University Non-Interventional Clinical Research Ethics Committee prior to patient enrollment (decision no: 25, date: 02.05.2013).

Informed Consent: Allergic patients who met the study criteria were included in the study group after verbal consent was obtained from themselves or their relatives.

Footnotes

Author Contributions

Concept Design – F.M.S., M.E.; Data Collection or Processing – F.M.S., H.K.S; Analysis or Interpretation – F.M.S., H.K.S., M.E.; Literature Review – F.M.S., Y.B., M.E.; Writing, Reviewing and Editing – F.M.S., Y.B., M.E.

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REFERENCES

1. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-1414. [CrossRef]
2. Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. *World Allergy Organ J*. 2020;13(10):100472. [CrossRef]
3. Campbell RL, Li JT, Nicklas RA, Sadosty AT; Members of the Joint Task Force; Practice Parameter Workgroup. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. *Ann Allergy Asthma Immunol*. 2014;113(6):599-608. [CrossRef]
4. Klein JS, Yocum MW. Underreporting of anaphylaxis in a community emergency room. *J Allergy Clin Immunol*. 1995;95(2):637-638. [CrossRef]
5. Suresh S, Rajvanshi PK, Noguchi CT. The many facets of erythropoietin physiologic and metabolic response. *Front Physiol*. 2020;10:1534. [CrossRef]
6. Nairz M, Sonnweber T, Schroll A, Theurl I, Weiss G. The pleiotropic effects of erythropoietin in infection and inflammation. *Microbes Infect*. 2012;14(3):238-246. [CrossRef]
7. Brines M, Cerami A. Erythropoietin-mediated tissue protection: reducing collateral damage from the primary injury response. *J Intern Med*. 2008;264(5):405-432. [CrossRef]
8. Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. *J Interferon Cytokine Res*. 1998;18(8):555-559. [CrossRef]
9. Simons FE, Ardusso LR, Bilò MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J*. 2011;4(2):13-37. [CrossRef]
10. Pier J, Bingemann TA. Urticaria, angioedema, and anaphylaxis. *Pediatr Rev*. 2020;41(6):283-292. [CrossRef]
11. Olofsson K, Hellström S, Hammarström ML. Human uvula: characterization of resident leukocytes and local cytokine production. *Ann Otol Rhinol Laryngol*. 2000;109(5):488-496. [CrossRef]
12. Bahlmann FH, de Groot K, Haller H, Fliser D. Erythropoietin: is it more than correcting anaemia? *Nephrol Dial Transplant*. 2004;19(1):20-22. [CrossRef]
13. Tahan F, Akar HH, Dursun I, Yilmaz K. Desensitization of darbepoetin-α: a case report. *Eur Ann Allergy Clin Immunol*. 2013;45(5):176-177. [CrossRef]
14. Alexandre AF, Ali M, Lawrence A, McKendrick J. Delayed-type hypersensitivity reaction due to epoetin-alfa in CKD: a therapeutic challenge. *J Am Soc Nephrol*. 2021;32:189.
15. Brines M, Grasso G, Fiordaliso F, et al. Erythropoietin mediates tissue protection through an erythropoietin and common beta-subunit heteroreceptor. *Proc Natl Acad Sci U S A*. 2004;101(41):14907-14912. [CrossRef]