

Effects of Endogen Erythropoietin on Parathormone Secretion

Endojen Eritropoietinin Parathormon Salgısı Üzerine Etkileri

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ABSTRACT

Objective: We hypothesize that tissue hypoxia would increase erythropoietin, as well as parathormone (PTH), secretion. To verify this hypothesis, patients who had undergone orthopedic surgery with a pneumatic tourniquet were evaluated for endogenous tissue hypoxia.

Methods: This study included 20 patients who underwent orthopedic surgery with a pneumatic tourniquet, wherein, 6 had diagnostic arthroscopy and 14 had anterior cruciate ligament reconstruction. All operations were performed under spinal anesthesia. The paired t-test was used to detect the differences between serial concentrations of parathyroid hormone, erythropoietin, calcium, and phosphorus levels before and after ischemia, where "p values" of <0.05 were considered significant.

Results: The average duration of ischemia that patients were exposed to during surgery was 57.40±22.65 min. After ischemia, parathyroid hormone and erythropoietin levels were significantly elevated (p<0.001; p<0.001). No significant difference was found in calcium and phosphorus levels in patients before and after ischemia. A positive correlation was found between parathyroid hormone and erythropoietin levels (p<0.05).

Conclusion: Our study is the first to show that the increase in erythropoietin levels in response to tissue hypoxia and increases the release of PTH.

Keywords: Erythropoietin, parathormone, hypoxia, pneumatic tourniquet

ÖZ

Amaç: Hipotezimiz, doku hipoksisinin parathormon (PTH) kadar eritropoietin salgısını da artıracığıydı. Bu hipotezi doğrulamak için pnömatik turnike ile ortopedik cerrahi geçiren hastalar endojen doku hipoksisi açısından değerlendirildi.

Yöntem: Bu çalışmaya pnömatik turnike ile ortopedik cerrahi uygulanan 20 hasta dahil edildi. Altısına tanısal artroskopisi, 14'üne ön çapraz bağ rekonstrüksiyonu yapıldı. Ameliyatların tamamı spinal anestezi altında yapıldı. Paratiroid hormonu, eritropoietin, kalsiyum ve fosfor düzeylerinin iskemi öncesi ve sonrasındaki seri konsantrasyonları arasındaki farkların saptanması için eşleştirilmiş t-testini kullandık, burada "p değerlerinin" <0,05 olması anlamlı kabul edildi.

Bulgular: Hastaların ameliyat sırasında maruz kaldıkları ortalama iskemi süresi 57,40±22,65 dakika idi. İskemi sonrası paratiroid hormonu ve eritropoietin seviyeleri anlamlı olarak yükseldi (p<0,001; p<0,001). İskemi öncesi ve sonrası hastalarda kalsiyum ve fosfor düzeylerinde anlamlı bir fark yoktu. Paratiroid hormonu ile eritropoietin düzeyleri arasında pozitif korelasyon vardı (p<0,05).

Sonuç: Çalışmamız doku hipoksisine yanıt olarak eritropoietin düzeylerindeki artışın PTH salınımını artırdığını gösteren ilk çalışma olması ile ayırt edilmektedir.

Anahtar Kelimeler: Eritropoietin, parathormon, hipoksi, pnömatik turnike

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INTRODUCTION

Erythropoietin is a hormone that is primarily produced in the adult kidney and the liver of the fetus. The most important physiological function of erythropoietin is the maintenance of erythropoiesis in the bone marrow.¹

However, erythropoietin receptors, of which the physiological significance are not very well understood, exist in many tissues,^{2,3} such as the parathyroid gland.⁴ Erythropoietin receptors are found in parathyroid cells; however, the effect of endogenous erythropoietin secretion on parathormone (PTH) secretion is unknown.

A recent study showed high levels of PTH in patients with anemia.⁵ Another study showed elevated levels of erythropoietin in cases of primary hyperparathyroidism.⁶ These data suggest that increased endogenous erythropoietin stimulates PTH secretion.

The most important stimulant of erythropoietin is hypoxia.⁷ We hypothesize that tissue hypoxia will increase erythropoietin, which will increase the PTH secretion. To test this hypothesis, patients undergoing orthopedic surgery with pneumatic tourniquet application were evaluated for endogenous tissue hypoxia. Pneumatic tourniquet application has long been used in orthopedic surgery due to its advantages in providing a bloodless area and reducing blood loss.^{8,9} However, it causes ischemic damage and hypoxia at the tissue level.¹⁰ This study aimed to investigate the effects of tissue hypoxia on erythropoietin and PTH secretion in patients undergoing surgery with pneumatic tourniquet application.

METHODS

This study was conducted at the Van Regional Training and Research Hospital Orthopedics Clinic between May 2014 and July 2014. A total of 20 patients who had pneumatic tourniquet application were included to evaluate the effect of tissue hypoxia on erythropoietin and PTH secretion. Of the 20 patients, 6 underwent diagnostic arthroscopy and 14 had anterior cruciate ligament reconstruction. All operations were performed under spinal anesthesia. Cases that required

general anesthesia were excluded because of their potential effect on erythropoietin secretion. Similarly, patients with bone lesions were excluded because the manipulation could affect the calcium, phosphorus, and/or PTH secretion.

All data regarding the age and gender of patients and ischemia duration caused by pneumatic dilatation were recorded. Blood samples were taken after spinal anesthesia induction in all cases, both before and 20 min after pneumatic dilatation to determine calcium, phosphorus, PTH, and erythropoietin levels. Calcium and phosphorus levels were determined by a photometric method using the Modular 800 device, whereas PTH and erythropoietin levels were measured using a microparticulate chemiluminescence method with the Architect i2000SR device.

Statistical Analysis

Data from the study forms were recorded to a computer database, and statistical analysis was performed with Statistical Package for the Social Sciences 16 software. Laboratory results before and after ischemia were compared with the Student's t-test. The correlations were analyzed between variables using the Spearman correlation analysis. Results were presented as mean±standard deviation and a p value of <0.05 was regarded as statistically significant.

RESULTS

This study included 20 patients, of whom 70% were male and 30% were female. The mean age was 32.07±9.78, and 30% and 70% of patients underwent arthroscopy and anterior cruciate ligament operations, respectively. The mean duration that patients were exposed to ischemia during surgery was 57.40±22.65 min.

The pre- and post-ischemia laboratory findings of 20 patients in the study are shown in Table 1. A statistically significant increase was found in PTH and erythropoietin levels (p values for all parameters were <0.001). No statistically significant difference was found in pre- and post-ischemia calcium and phosphorous levels (p=0.970, p=0.073).

A positive correlation was shown in the correlation analysis between age and pre-ischemia erythropoietin levels and

	N	Pre-ischemia Mean±SD	Post-ischemia Mean±SD	p value
Erythropoietin (mIU/mL)	20	7.16±3.26	8.84±3.43	<0.001
Parathyroidhormone (pg/mL)	20	38.73±20.16	50.92±22.98	<0.001
Calcium (mg/dL)	20	9.22±0.65	9.21±0.59	0.970
Phosphorus (mg/dL)	20	3.77±0.55	3.83±0.59	0.073

SD: Standard deviation

age, pre-ischemia, and post-ischemia PTH levels, and post-ischemia erythropoietin levels (all $p < 0.01$). A positive correlation was also found between pre-ischemia PTH levels and age, pre- and post-ischemia erythropoietin levels, and post-ischemia PTH levels ($p < 0.05$, $p < 0.01$, $p < 0.01$, and $p < 0.01$, respectively). The calcium and phosphorous levels measured before pneumatic dilatation positively correlated with post-ischemia calcium and phosphorous levels (all $p < 0.01$). In addition, correlation analysis revealed that PTH increase due to ischemia correlated with erythropoietin increase ($p < 0.05$). The Spearman correlation analyses of all parameters are shown in Table 2.

DISCUSSION

This study demonstrates that tissue hypoxia in patients operated on with pneumatic dilation increases erythropoietin and PTH levels. In addition, increased erythropoietin levels were correlated with increased PTH levels. The relationship between erythropoietin and PTH could not be fully explained. Anemia may develop early in the course of chronic kidney disease and is nearly universal in patients with stage 5 chronic kidney disease. The influence of PTH on erythropoiesis is mainly due to anemia and secondary hyperparathyroidism observed in patients with uremia.^{11,12} Likewise, *in vitro* studies on mice demonstrated that high PTH concentrations could inhibit erythropoiesis.^{13,14} Contrarily, *in vitro* studies, failed to prove the influence of PTH on human hematopoietic stem cells.^{15,16}

Myelofibrosis is thought to be a pathogenetic cause of anemia in primary and secondary hyperparathyroidism; however, data are controversial. Meytes et al.¹⁷ failed to show the existence of a proliferative effect of PTH on bone marrow fibroblasts in an *in vitro* study. Nevertheless, case presentations of primary hyperparathyroidism and myelofibrosis are reported, wherein myelofibrosis was resolved after parathyroidectomy.^{18,19} In light of these data, Bhadada et al.²⁰ showed bone marrow fibrosis in half of the cases of primary hyperparathyroidism and anemia, and the anemia and myelofibrosis were resolved after parathyroidectomy.

Erythropoietin levels in primary hyperparathyroidism were also studied due to the relationship between elevated PTH levels and anemia. Kokot et al.⁶ showed elevated erythropoietin levels in patients

Table 2. The Spearman correlation analysis of the measured parameters

	Pre-EPO	Pre-PTH	Pre-Ca	Pre-P	IT	Age	Post-EPO	Post-PTH	Post-CA	Post-P	Post-pre EPO	Post-pre PTH	Post-pre Ca	Post-pre P
Pre-EPO	1.000													
Pre-PTH	0.811**	1.000												
Pre-Ca	0.029	0.132	1.000											
Pre-P	-0.021	0.107	0.011	1.000										
IT	0.004	-0.134	-0.064	0.181	1.000									
Age	0.707**	0.610*	-0.148	0.145	0.193	1.000								
Post-EPO	0.879**	0.661**	0.243	0.139	0.082	0.580*	1.000							
Post-PTH	0.857**	0.829**	0.121	-0.118	-0.075	0.538*	0.786**	1.000						
Post-CA	-0.075	-0.014	0.882**	0.139	-0.132	-0.191	0.171	-0.125	1.000					
Post-P	0.179	0.307	-0.036	0.889**	0.175	0.331	0.246	0.136	0.014	1.000				
Post-pre EPO	0.007	-0.011	0.271	0.296	0.268	0.009	0.414	0.182	0.139	0.257	1.000			
Post-pre PTH	0.418	0.068	0.021	0.068	0.098	0.284	0.646**	0.446	-0.082	0.061	0.589*	1.000		
Post-pre Ca	-0.046	-0.314	-0.236	0.118	-0.091	0.036	-0.050	-0.411	0.204	0.014	-0.421	-0.118	1.000	
Post-pre P	0.371	0.368	-0.343	-0.061	0.073	0.512	0.239	0.414	-0.382	0.357	0.039	0.011	-0.036	1.000

* $p < 0.05$, ** $p < 0.01$.

Pre: Pre-ischemia, Post: Post-ischemia, PTH: Parathyroid hormone, EPO: Erythropoietin, Ca: Calcium, P: Phosphorus, IT: Ischemia time

with primary hyperparathyroidism, which related it to renal dysfunction and anemia observed in patients with primary hyperparathyroidism. However, this study failed to completely evaluate the cause-effect relationship; erythropoietin elevation can also be a result of increased PTH. Thus in 2007, Oztürk et al.⁴ demonstrated the existence of erythropoietin receptors in parathyroidectomy specimens although the effect of these receptors on PTH secretion is unknown. Atmaca and Tasdemir⁵ revealed elevated levels of PTH in patients with deficiency anemia as a reflection of this. Our study detected increased levels of both erythropoietin and PTH after ischemia ($p < 0.01$). The unchanged calcium and phosphorus levels support the proposed influence of erythropoietin on PTH secretion.

Study Limitations

The small number of patients and the single-center study are our main limitations.

CONCLUSION

Our study is remarkable since, for the first time, it revealed that increased erythropoietin levels due to tissue hypoxia stimulate PTH secretion.

Ethics

Ethics Committee Approval: The study were approved by the Van Yüzüncü Yıl University of Local Ethics Committee (date/protocol no: 18.04.2014/06).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.G., C.A., M.A., M.F.Ö., Concept: E.G., E.K., M.A., Design: E.G., S.Ö., C.A., Data Collection or Processing: C.A., E.K., M.F.Ö., Analysis or Interpretation: E.G., C.A., S.Ö., E.K., Literature Search: E.G., C.A., M.F.Ö., E.K., Writing: E.G., C.A., M.A.

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