ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Investigation of the Effect of Parathyroid Hormone on Corneal Clarity

Paratiroid Hormonun Kornea Saydamlığı Üzerine Etkisinin İncelenmesi

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ABSTRACT Objective: To evaluate the corneal clarity of the patients with surgically induced hypoparathyroidism (SIH) and compare these results with those of age-matched healthy control subjects. **Material and Methods:** Fourty six female patients with SIH and 36 age-matched healthy female subjects were enrolled in this prospective study. In order to evaluate the corneal clarity of the patients, corneal densitometry was measured with densitometry software of Scheimpflug corneal topography (Pentacam® HR, Wetzlar, Germany). For densitometry analysis, the 12-mm diameter area of the cornea was subdivided into four concentric radial zones (0 to 2, 2 to 6, 6 to 10, 10 to 12 mm) and also into anterior, central, and posterior layers based on corneal depth. Corneal densitometry measurements were examined, and only the data from the right eyes of the participants were used for statistical analysis. **Results:** The corneal densitometry measurements of the SIH and control group were similar for all concentric radial zones and corneal depths except the central 0-2 mm (p=0.011), posterior 0-2 mm (p=0.003), posterior 2-6 mm (p=0.011) and total thickness 0-2 mm (p=0.028), of all were statistically significantly lower in SIH group. There was a statistically significant positive correlation between the posterior 10-12 mm corneal densitometry and serum parathyroid hormone levels in the SIH group (p=0.024; r=0.321). **Conclusion:** This study shows that the corneal clarity of the patients with SIH subjects under the sufficient postoperative treatment was similar when compared to the healthy control.

Keywords: Calcium; corneal densitometry; hypoparathyroidism

ÖZET Amaç: Bu çalışmada, cerrahi olarak indüklenen hipoparatiroidizmi olan hastaların kornea saydamlığını değerlendirmek ve bu sonuçları, yaş uyumlu sağlıklı kontrol grubuyla karşılaştırmak amaçlanmıştır. **Gereç ve Yöntemler:** Prospektif olarak düzenlenen bu çalışmaya, cerrahi olarak indüklenen hipoparatiroidizmi olan 46 kadın hasta ile yaş uyumlu 36 sağlıklı kadın gönüllü dâhil edildi. Hastaların kornea saydamlığı, Scheimpflug kornea topografisinin (Pentacam® HR, Wetzlar, Almanya) kornea dansitometrisi özelliği kullanılarak belirlendi. Dansitometri analizi için 12 mm'lik kornea alanı 4 eş merkezli radyal bölgeye (0-2, 2-6, 6-10, 10-12 mm) ve kornea kalınlığına göre anterior, santral ve posterior katmanlara ayrıldı. Kornea dansitometri ölçümleri incelendi ve istatistiksel analiz için katılımcıların sadece sağ gözlerinden alınan veriler kullanıldı. **Bulgular:** Cerrahi olarak indüklenen hipoparatiroidizm grubunda istatistiksel olarak anlamlı düşük saptanan santral 0-2 mm (p=0,011), posterior 0-2 mm (p=0,003), posterior 2-6 mm (p=0,011) korneal dansitometri ve toplam korneal kalınlık 0-2 mm (p=0,028) değerleri dışındaki diğer ölçümler, kontrol grubu ile benzerdi. Hipoparatroidizm grubunda 10-12 mm korneal dansitometri değeri ile serum paratiroid hormon düzeyi arasında istatistiksel olarak anlamlı pozitif korelasyon saptandı (p=0,024; r=0,321). **Sonuç:** Bu çalışma, cerrahi olarak indüklenen hipoparatiroidizmi olan hastaların kornea saydamlığının, yeterli postoperatif tedavi altında sağlıklı kontroller ile benzer olduğunu göstermektedir.

Anahtar Kelimeler: Kalsiyum; korneal dansitometri; hipoparatiroidizm

Hypoparathyroidism, characterized by insufficient serum concentrations of parathyroid hormone (PTH), is one of the common endocrinological disorders. Insufficient serum PTH leads to hypocalcemia and hyperphosphataemia.[1] Agenesis/dysgenesis of parathyroid glands, autoimmune diseases and previous neck surgery may be the cause of hypoparathyroidism. The most common cause of acquired

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hypoparathyroidism is damage to parathyroid glands during neck surgery, namely surgically induced hypoparathyroidism (SIH).[2] Powers et al. reported that 7.6% of 110,000 neck surgeries resulted with hypoparathyroidism.[3] Inadequate secretion of PTH can affect several organ systems, including renal, neurological, skeletal, cardiovascular and also ocular structures.

The standard of care in postsurgical hypoparathyroidism is treatment with oral calcium and vitamin D however, the treatment cannot completely replace the functions of normal serum PTH.[4] Calcium status of the patient and disease duration usually determine the severity of complications in hypoparathyroidism.[2] It has been known that calcium concentration imbalance in the aqueous humor may affect the epithelial cells of the human crystalline lens, resulting in cataract formation.[5,6] Additionally, serum calcium levels, especially hypercalcemia, have various effects on the cornea and corneal wound healing process.[7-9]

Densitometry software of Scheimpflug corneal topography systems enable quantitative measurement of corneal clarity. These corneal densitometry measurements, which are assumed to be good indicators of corneal health, provide information about corneal transparency.[10] The primary sources of corneal light backscattering are corneal epithelium and endothelium layers, and corneal endothelium morphology was found to be correlated with corneal densitometry.[11] Corneal irregularities which increased light backscattering can affect the corneal function and visual acuity.[10] Additionally, several factors such as age, corneal edema and ectatic corneal disorders can affect corneal clarity and corneal densitometry measurements owing to increased light backscattering.[12-14]

The aim of the present study was to evaluate the corneal clarity, by using corneal densitometry measurements, of the patients with SIH who have clinically clear corneas.

MATERIAL AND METHODS

PARTICIPANTS

Fourty six female patients with the diagnosis of SIH and 36 age-matched healthy women were enrolled in this prospective case-control study. The study was approved by the Ankara Training and Research Hospital Institutional Ethics Committee (Number: E-19-142, date: 20.2.2020) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all of the participants.

The SIH was diagnosed based on the low calcium, high phosphate, and low serum PTH levels with normal renal function after neck surgery. Serum calcium, inorganic phosphorus, thyroid-stimulating hormone and PTH levels at the day of the ophthalmologic evaluation were recorded in SIH group. All patients with SIH were using elemental calcium, activated vitamin D and levothyroxine.

OCULAR EXAMINATION

Best-corrected visual acuity (BCVA) with Snellen chart, anterior segment examination with slit-lamp biomicroscopy, intraocular pressure measurement with non-contact tonometry, and dilated fundus examination were performed in all subjects.

EXCLUSION AND INCLUSION CRITERIA

Subjects without a history of any ocular problem and with a BCVA equal to 1.0 according to the Snellen chart were included in the study. Patients with a history of any systemic disease other than hypoparathyroidism, ocular trauma or surgery, smoking, and contact lens use were excluded. Participants with a spherical equivalent of refractive error >1.00 diopter and central corneal thickness (CCT) >600 µm were also excluded. Additionally, patients with abnormal serum thyroid-stimulating hormone level (out of range, 0.4-3.7 mIU/L) and symptoms of hypothyroidism were excluded from the study.

CORNEAL DENSITOMETRY MEASUREMENTS

Cornea and the anterior chamber were examined by the same experienced clinician using the Pentacam HR® (Oculus Optikgeräte GmbH, Wetzlar, Germany). The room lights were switched off to obtain a reflex-free image and dim-light conditions. Before the examination, the patient sat in front of the Scheimpflug camera, put her chin on a chinrest and pushed her foreheads into the bar. The patient looked

at a black fixation target when a suitable position was provided. Scans with a quality factor of less than 95% were excluded from the study. In order to minimize the effect of corneal diurnal changes, Scheimpflug imaging was performed at the same period of the day (between 14:00 to 16:00).

Corneal densitometry was measured using the densitometry software, which divides the 12 mm diameter of cornea into four concentric zones and three layers in depth. The first concentric zone is an area of two millimeters in diameter in the central cornea. The other zones are predefined 2-6 mm, 6-10 mm, and 10-12 mm annular areas around the first zone. The three layers of corneal depth includes anterior 120 µm (outermost), posterior 60 µm (innermost) and central (between anterior and posterior layers). The corneal densitometry values, range between 0 (transparent) to 100 (opaque), are calculated automatically and are expressed in grayscale units (Figure 1). Additionally, curvature, volume and thickness of cornea and depth, volume and angle of the anterior chamber were analysed using Pentacam® HR. The measurements of right eyes were used for statistical analysis.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS version 24.0, SPSS Inc., Chicago, Illinois, USA) software was used for statistical analysis. Analytical (Kolmogorov-Smirnov/Shapiro-Wilk test) tools were used to detect the distribution pattern of the variables. While comparing the study groups, the student t-test was used for normally distributed data and the Mann-Whitney U test was used for non-normally distributed data. The correlations were detected using the Pearson correlation coefficient. Statistical significance was assessed as $p<0.05$.

RESULTS

Fourty six female patients with the diagnosis of SIH (mean age, 45.6±10.4 years; age range, 20-71 years) and 36 age-matched healthy women (mean age, 47.0±7.6 years; age range, 34-65 years) were enrolled in the study (p=0.506).

The mean serum calcium, phosphorus and PTH levels of patients with SIH were 8.9±0.8 mg/dL (range, 6.9-10.5 mg/dL), 4.2±0.7 mg/dL (range, 2.9-6.6 mg/dL), 16.8±8.7 ng/L (range, 5.0-38.9 ng/L), respectively. The mean postsurgical period was 8.6±5.7 years (range, 1-22 years) in the SIH group.

Table 1 shows the Scheimpflug corneal topography parameters of the SIH and control groups. The mean values of curvatures and volume of cornea and volume, angle of anterior chamber showed no significant difference (p>0.05 for all parameters). Anterior chamber depth (ACD) was lower in the SIH group (p=0.013). There was no significant difference in the mean value of CCT between the SIH (542.6±33.7

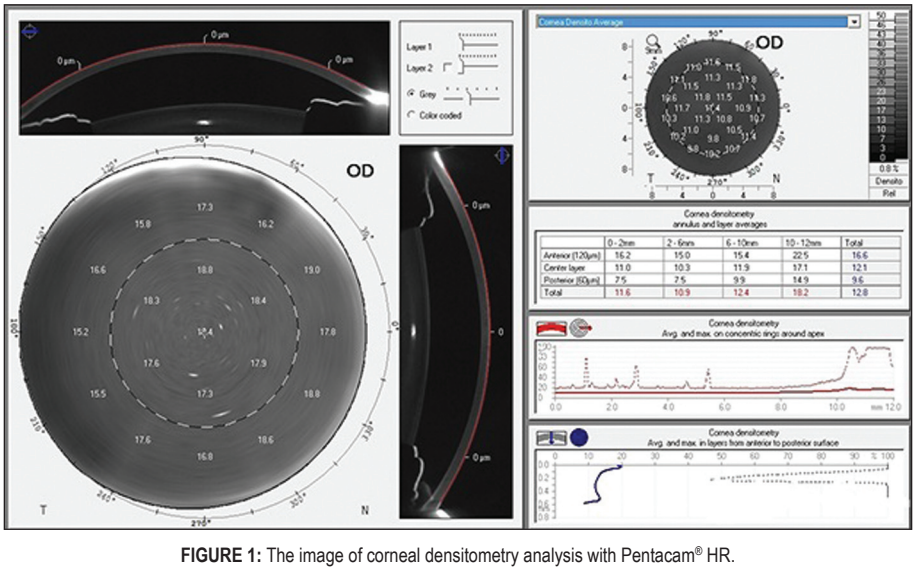

FIGURE 1: The image of corneal densitometry analysis with Pentacam® HR.

TABLE 1: Comparison of the Scheimpflug corneal parameters.

	Surgically induced hypoparathyroidism group (n=46)	Healthy control group (n=36)	p value
Spherical equivalent, D	0.13±0.61	0.07±0.57	0.107[a]
Anterior cornea			
Kmin, D	42.9±1.4	43.1±1.5	0.652[a]
Kmax, D	43.8±1.4	44.0±1.4	0.560[a]
Kmean, D	43.3±1.4	43.5±1.4	0.554[a]
Posterior cornea			
Kmin, D	5.3±2.9	6.1±0.2	0.121[a]
Kmax, D	6.1±1.8	6.4±0.2	0.357[a]
Kmean, D	6.2 (5.8-6.8)	6.2 (5.7-6.6)	0.935[b]
Apex pachymeter, µm	542.6±33.7	529.0±30.0	0.057[a]
Thinnest pachymeter, µm	536.8±33.6	523.8±30.1	0.068[a]
Cornea volume, mm3	61.1±10.2	58.5±3.7	0.154[a]
Anterior chamber depth, mm	2.75±0.28	2.92±0.33	0.013[a]
Anterior chamber volume, mm3	153.4±31.3	165.3±35.4	0.101[a]
Anterior chamber angle, degree	30.4±7.8	30.0±7.9	0.835[a]
White to white, mm	11.8±0.3	11.8±0.3	0.512[a]

[a]Student t-test; [b]Mann-Whitney U test. Normally distributed variables are presented as mean±standard deviation, and non-normally distributed variables are presented as median (minimum-maximum). Bold values indicate statistically significant.

µm; range, 450.0-595.0 µm) and control groups (529.0±30.0 µm; range, 463.0-587.0 µm) (p=0.057).

The corneal densitometry measurements in all concentric radial zones and different corneal depths are shown in Table 2. The corneal densitometry measurements of central 0-2 mm, posterior 0-2 mm, posterior 2-6 mm, and total thickness 0-2 mm were statistically significantly lower in the SIH group (p<0.05 for all). In the SIH group, there was a statistically significant positive correlation between the posterior 10-12 mm corneal density and serum PTH level (r=0.321, p=0.024; Table 3).

DISCUSSION

In the present study, the densitometry software of Scheimpflug imaging system was used in order to obtain objective and repeatable measurements depicting the corneal clarity of patients with SIH and clinically clear corneas. The ideal system for measurement of corneal clarity should contain quantitative data and should be objective and reproducible. The Pentacam® HR is a quantitative and objective method to determine corneal transparency and clarity.[15]

Corneal densitometry measurements ensure information about the clarity of the cornea.[10] The corneal transparency is provided by the regular stromal collagen fibrils and the situation of corneal hydration.[16,17] Both the endothelial and epithelial layers of the cornea are the significant sources of corneal light backscattering; thus normal function of these two layers is essential for corneal clarity. Tekin et al. investigated the corneal densitometry and corneal endothelium in healthy subjects and determined that the endothelial cell density and the percentage of hexagonal cells were inversely correlated with the corneal densitometry.[11] Additionally, corneal disorders such as scars, edema, and infiltrates can affect corneal clarity and measurements of corneal densitometry.[13,18]

Primary hypoparathyroidism has several ocular complications such as cataract and papilledema.[19] Previous studies failed to find a causal relationship between postsurgical hypoparathyroidism and cataract formation however, Daba et al. reported a case with bilateral hypocalcemic cataract after total thyroidectomy.[20,21] Matsushima et al. found that calcium concentration imbalance in the crystalline lens and aqueous humor may affect the epithelial cells of the human lens, resulting in cataract.[6]

The calcium signalling is involved in physiological processes such as cell proliferation, survival, and apoptosis.[22,23] Also, calcium plays an essential

TABLE 2: Comparison of the corneal densitometry measurements in surgically induced hypoparathyroidism and control groups.

	Surgically induced hypoparathyroidism group (n=46)	Healthy control group (n=36)	p value
Anterior 120 µ			
0-2 mm	16.1 (12.4-23.0)	16.2 (14.6-20.0)	0.441b
2-6 mm	14.9 (12.0-20.7)	14.8 (12.9-18.6)	0.761b
6-10 mm	16.9±3.7	17.0±3.4	0.976a
10-12 mm	25.9±8.0	27.3±8.2	0.457a
Total diameter	17.8±2.8	17.9±2.4	0.882a
Central			
0-2 mm	10.8 (9.7-14.9)	11.2 (9.8-14.1)	0.011b
2-6 mm	9.8 (9.0-13.6)	10.3 (8.9-13.4)	0.056b
6-10 mm	11.9±2.1	12.3±2.5	0.507a
10-12 mm	16.2±3.7	17.2±3.7	0.229a
Total diameter	11.4 (9.4-15.9)	11.8 (9.3-15.4)	0.351b
Posterior 60 µ			
0-2 mm	8.1 (7.2-11.6)	8.6 (7.3-12.5)	0.003b
2-6 mm	7.7 (6.8-10.4)	8.0 (7.0-12.1)	0.011b
6-10 mm	9.9±1.6	10.5±2.0	0.172a
10-12 mm	13.5±2.6	13.6±2.4	0.957a
Total diameter	9.5±1.2	10.0±1.5	0.134a
Total thickness			
0-2 mm	11.6 (10.6-16.3)	12.1 (10.8-15.3)	0.028b
2-6 mm	10.8 (9.8-14.9)	11.0 (9.8-14.5)	0.100b
6-10 mm	12.4 (9.6-28.3)	12.9 (9.5-19.2)	0.851b
10-12 mm	18.8±4.2	19.3±4.4	0.560a
Total diameter	12.9±1.5	13.3±1.7	0.356a

[a]Student t-test; [b]Mann-Whitney U test. Normally distributed variables are presented as mean±standard deviation, and non-normally distributed variables are presented as median (minimum-maximum). Bold values indicate statistically significant.

role in the endothelium and epithelium wound healing processes.[24,25] Chifflet et al. found that increased intracellular calcium in wound border cells which present in the bovine corneal endothelium may play a role in the healing process and inhibition of this process delays wound healing.[26] Nagai et al. found that hypercalcemia affects the viability of both human and rat corneal epithelial cells.[9] Additionally, Korkiamäki et al. predicated that differences between healthy and type-1 neurofibromatosis keratinocytes were dependent on extracellular calcium concentration.[27] As mentioned above, calcium plays an important role in maintaining normal corneal function, and serum calcium imbalance may have detrimental effects on corneal structures. Based on above-aforementioned studies, it was thought that cornea might be affected in hypoparathyroidism, in which calcium imbalance is observed due to low serum PTH levels and use of oral calcium, because the treatment (calcium and vitamin D) cannot fully replace the functions of normal serum PTH.[4]

Serum calcium imbalance can be common in parathyroid gland disorders and chronic kidney failure. Sati et al. investigated corneal endothelial changes in patients with chronic kidney failure and found that CCT and endothelial cell density were lower in chronic kidney failure group compared to the healthy group.[28] Also, they did not find any correlation between endothelial parameters and serum calcium and suggested that these insignificant correlations may occur owing to the well-controlled calcium condition. In contrast to this study, calcium hydroxyapatite precursors were found in the corneal endothelium via electron microscopy in patients with primary hyperparathyroidism by Jensen.[29] Additionally, calcium deposits in the cornea were shown in diseases such as Fanconi' syndrome and juvenile idiopathic arthritis-associated uveitis.[30-32]

TABLE 3: Correlations between the clinical and laboratory findings and corneal densitometry values of patients with surgically induced hypoparathyroidism.

Corneal densitometry	Serum calcium	Serum phosphorus	Serum parathyroid hormone	Hypoparathyroidism duration
Anterior 120 µ				
0-2 mm	r=0.162	r=-0.246	r=0.036	r=0.087
	p=0.266	p=0.088	p=0.809	p=0.554
2-6 mm	r=0.057	r=-0.123	r=0.080	r=0.170
	p=0.699	p=0.402	p=0.586	p=0.243
6-10 mm	r=0.073	r=0.129	r=0.015	r=-0.019
	p=0.618	p=0.376	p=0.919	p=0.895
10-12 mm	r=0.132	r=0.041	r=-0.102	r=0.086
	p=0.366	p=0.782	p=0.487	p=0.558
Total diameter	r=0.085	r=0.046	r=-0.005	r=0.037
	p=0.563	p=0.755	p=0.971	p=0.801
Central				
0-2 mm	r=0.079	r=-0.062	r=0.054	r=0.203
	p=0.588	p=0.674	p=0.715	p=0.163
2-6 mm	r=0.078	r=-0.021	r=0.028	r=0.223
	p=0.596	p=0.886	p=0.850	p=0.123
6-10 mm	r=0.065	r=0.198	r=0.025	r=0.052
	p=0.658	p=0.173	p=0.867	p=0.722
10-12 mm	r=-0.015	r=0.073	r=0.085	r=0.106
	p=0.918	p=0.616	p=0.560	p=0.468
Total diameter	r=0.020	r=0.103	r=0.116	r=0.076
	p=0.894	p=0.479	p=0.429	p=0.605
Posterior 60 µ				
0-2 mm	r=0.162	r=0.053	r=-0.020	r=0.153
	p=0.267	p=0.717	p=0.892	p=0.295
2-6 mm	r=-0.007	r=0.099	r=-0.037	r=0.198
	p=0.962	p=0.500	p=0.800	p=0.173
6-10 mm	r=0.013	r=0.174	r=0.029	r=0.089
	p=0.927	p=0.231	p=0.844	p=0.542
10-12 mm	r=0.030	r=-0.050	**r=0.321**	r=0.141
	p=0.841	p=0.734	**p=0.024**	p=0.335
Total diameter	r=-0.050	r=0.140	r=0.140	r=0.057
	p=0.731	p=0.338	p=0.337	p=0.696
Total thickness				
0-2 mm	r=0.141	r=-0.171	r=0.052	r=0.167
	p=0.334	p=0.241	p=0.721	p=0.251
2-6 mm	r=0.042	r=-0.044	r=0.009	r=0.252
	p=0.775	p=0.765	p=0.952	p=0.081
6-10 mm	r=0.116	r=0.083	r=0.074	r=0.080
	p=0.428	p=0.570	p=0.612	p=0.583
10-12 mm	r=0.082	r=0.033	r=0.035	r=0.098
	p=0.577	p=0.824	p=0.813	p=0.504
Total diameter	r=0.026	r=0.126	r=0.088	r=0.203
	p=0.861	p=0.400	p=0.556	p=0.171

Bold values indicate statistically significant correlations.

The present study showed that the patients with SIH had similar values with the control group in parameters, including corneal curvatures, corneal thickness, corneal volume, anterior chamber volume and

anterior chamber angle. The ACD was found to be lower in the SIH group however, it is not clear if this statistically significant difference has any clinical significance. The corneal densitometry measurements of the SIH and control group were similar for all concentric radial zones and corneal depths except the central 0-2 mm, posterior 0-2 mm, posterior 2-6 mm and total thickness 0-2 mm, of all were statistically significantly lower in SIH group. However, it is not also clear if this statistically significant difference has any clinical significance; but at least, this study revealed that the patients with SIH do not have any increase in corneal densitometry. Additionally, this study showed that the corneal clarity was not affected in patients with SIH who were treated by elemental calcium and activated vitamin D.

A thorough search of the literature has not yielded any articles investigating the effect of SIH on corneal clarity. The authors consider the use of a quantitative and standardized imaging method to obtain objective measurements is the strength of this study. However, this study has several numbers of limitations. First of these, hypothyroidism is another condition which may play a role for changing corneal clarity; because corneal topographic fluctuations associated with exacerbated hypothyroidism were found in the literature.[33,34] However, the patients with abnormal thyroid function test were excluded from the study to minimize the effect of hypothyroidism on the cornea. Another limitation of the study can be the effect of dry eye disease on corneal clarity. The patients with a history of dry eye disease and chronic topical eye drop use were excluded, but ocular surface was not evaluated by using Schirmer test or tear breakup time. Another limitation of the present study is that specular microscopy was not used in order to detect the status of the corneal endothelium which can affect the corneal clarity, however participants with CCT >600 μm were excluded from the study to minimize the effect of endothelial dysfunction. It can be speculated that long-term follow-up studies can be performed in future, which should aim to evaluate corneal endothelial cell function with additional specular microscopy.

CONCLUSION

This study quantitatively demonstrated that corneal clarity of the patients with SIH was not lower compared to normal participants, in other words, the imbalance of serum calcium levels due to low serum PTH did not seem to lead to any loss in corneal clarity under the adequate postoperative treatment.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mehmet Ali Şekeroğlu;* ***Design:*** *Mehmet Ali Şekeroğlu;* ***Control/Supervision:*** *Mehmet Ali Şekeroğlu, Şerife Mehlika Kuşkonmaz;* ***Data Collection and/or Processing:*** *Ali Mert Koçer, Çağatay Emir Önder;* ***Analysis and/or Interpretation:*** *Ali Mert Koçer, Mehmet Ali Şekeroğlu;* ***Literature Review:*** *Ali Mert Koçer;* ***Writing the Article:*** *Ali Mert Koçer, Mehmet Ali Şekeroğlu;* ***Critical Review:*** *Mehmet Ali Şekeroğlu, Şerife Mehlika Kuşkonmaz.*

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