ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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# EVALUATION OF THE ASSOCIATION OF PIGMENTARY MACULOPATHY IN PRIMARY BLADDER PAIN SYNDROME PATIENTS RECEIVING PENTOSAN POLYSULFATE SODIUM TREATMENT

## PENTOSAN POLİSÜLFAT SODYUM TEDAVİSİ ALAN PRİMER MESANE AĞRISI SENDROMU HASTALARINDA PİGMENTER MAKULOPATİ İLİŞKİSİNİN DEĞERLENDİRİLMESİ

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## Öz

### Amaç

Primer mesane ağrı sendromu (PMAS); suprapubik bölgede ağrı, sık idrara çıkma, ani sıkışma hissi ve nokturi gibi alt üriner sistem semptomlarının en az birinin 6 haftadan uzun bir süre eşlik etmesi olarak tanımlanmaktadır. Primer mesane ağrı sendromu tedavisinde birçok alternatif tedavi olmasına rağmen oral olarak onaylanan tek ilaç pentosan polisülfat sodyumdur (PPS). Yaygın kullanımı sonrasında retinal toksiteyle ilişkilendirilmesinden dolayı çalışmamızda PPS kullanımı ile makulopati arasındaki ilişkiyi değerlendirmeyi amaçladık.

### Gereç ve Yöntem

2010-2020 yılları arasında tek merkezli PMAS tanısı alıp sadece PPS kullanımından fayda görebilecek alt grup ve fenotip değerlendirmesi (üriner ve non-ülseratif organa özgü alt gruplar) sonucunda çalışmaya dahil edildi. Çalışmadan özgeçmişinde dejeneratif makulopatisi olan veya makulopatiye yatkınlık yaratan hastalıkları olanlar çalışmadan çıkarılmışlardır. Hastalara Snellen görme eşeli ile düzeltilmiş en iyi görme keskinliği ölçümü, slit lamp biyomikroskop ile ön segment ve fundus incelemesi yapıldı ve göz içi basınçları ölçüldü. Renkli görme testi, arka segment optik koherans incelemesi ve10-2 görme alanı testi uygulandı ve fundus renkli ve otofloresans fotoğrafları çekildi. Düzeltilmiş en iyi görme keskinliği, renkli görme sonuçları, makula, koroid ve ortalama retina sinir lifi kalınlıkları, görme alanı ortalama sapma değeri ve fundus bulguları kaydedildi.

### Bulgular

Çalışmaya dahil edilen toplam 15 hastanın 4'ü (%37,5) erkek, 11'i (%73,3) kadındı. Hastaların yaş ortalamaları 53,3±11,2 olarak gözlendi. Takipleri sırasında ortalama oral PPS kullanım süresi 33,01±10,59 ay ve kümülatif oral PPS dozu 216,02±97,63 gr tanı süreleri ise 66,64±39,37 ay olarak tespit edilmiştir. Hastaların ortalama merkezi makula ve koroid kalınlığı sırasıyla

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254,55±33,11 mikron, 261,82±34,22 mikron olarak ölçüldü. Hastaların görme alanı sapma değeri ortalaması-1,89±-1,25 dB, fundus-otofloresans görüntülerinde ortalama retina sinir lif kalınlığı ise 98,1±17,62 mikron ölçüldü. Ek olarak çalışmamızda ortalama kümülatif dozun ve maruziyet süresinin altında ve üstündeki hastaların da göz bulguları kendi içinde karşılaştırıldı.

**Sonuç**
Çalışmamızda kronik PPS kullanımı ile makulopati arasında bir ilişki saptanmamıştır. Hasta grubunun oluşturulmasında; diyabet ve hipertansiyon gibi ek hastalıkları olan hastaların çıkartılması, fenotip ve alt grup değerlendirmesi sonucunda homojen bir şekilde oluşturulması son derece önemlidir.

**Anahtar Kelimeler:** Tedavi, Pentosan Polisülfat Sodyum, Pigmenter Makulopati, Primer Mesane Ağrı Sendromu, Yan Etki

## Abstract

**Objective**
Primary bladder pain syndrome (PBPS) is characterized with suprapubic pain accompanied by at least one lower urinary tract symptoms including frequent urination, urinary urgency and nocturia for more than 6 weeks. While there are many alternative therapies for the treatment of PBPS, the only approved oral medication is PPS (pentosan polysulfate sodium). As it has been associated with retinal toxicity after its widespread use, this study aims to evaluate the relationship between PPS use and maculopathy.

**Material and Methods**
The patients diagnosed with PBPS between 2010 and 2020 who may only benefit from PPS use were included into the study after subgroup and phenotype assessment (urinary and non-ulcerative organ-specific subgroups). In our study, patients who had history of degenerative maculopathy or diseases predisposing to maculopathy (age-related macular degeneration, diabetes mellitus, hypertension, chronic vascular disorders, central serous chorioretinopathy, retinal dystrophy, epiretinal membrane, and chronic exposure to hydroxychloroquine) were excluded to prevent possible misdirection. Patients underwent best-corrected visual acuity assessment using Snellen chart, anterior segment and fundus examination using slit lamp biomicroscopy, and intraocular pressure measurement. Color vision test (Ishihara test), posterior segment optical coherence examination and 10-2 visual field test were performed, and color images of the fundus and autofluorescence imaging were obtained. Best-corrected visual acuity, color vision results, macular, choroidal and mean retinal nerve fiber thicknesses, mean deviation of the visual field and fundus findings were recorded.

**Results**
Out of 15 patients included into the study, 4 (37.5%) were male and 11 (73.3%) were female. The mean age of the patients was 53.3±11.2 years. During the follow-up, the duration of oral PPS use was found to be 33.01±10.59 months, cumulative oral PPS dose to be 216.02±97.63 g and duration of diagnosis to be 66.64±39.37 months. The mean central macular thickness of the patients was measured to be 254.55±33.11 µm, and the mean choroidal thickness to be 261.82±34.22 µm. Mean deviation of the visual field of the patients was found to be -1.89 ±-1.25 dB. The mean retinal nerve fiber thickness was measured to be 98.1±17.62 µm from the fundus autofluorescence images of the patients. Furthermore, in the present study, the ocular findings of the patients who are at below and above the mean cumulative dose and exposure period were compared.

**Conclusion**
This study detected no correlation between long-term PPS use and maculopathy. When forming the patient group; it is crucial to exclude patients with comorbidities such as diabetes mellitus and hypertension, and to form a homogeneous group by phenotype and subgroup assessment. Randomized, prospective, multi-center studies are needed to better assess this correlation.

**Keywords:** Pentosan Polysulfate Sodium, Pigmentary Maculopathy, Primary Bladder Pain Syndrome, Side Effects, Treatments

## Introduction

Primary bladder pain syndrome (PBPS) is defined as perineal pain or discomfort, mainly in the suprapubic region, accompanied by at least one lower urinary tract symptoms including frequent urination, urinary urgency and nocturia for more than 6 weeks. (1) This condition is characterized with exacerbation of pain and urgency with bladder filling. The prevalence varies between 0.06% and 30% (2,3). It is seen 10-

fold more in females with no effect of ethnic factors on the prevalence. (4-6) The first-line treatment in PBPS consists of lifestyle changes and behavioral therapies. Other treatment options include oral medical therapies (pentosan polysulfate sodium (PPS), amitriptyline), intra-vesical therapies (PPS, hyaluronic acid, and chondroitin sulfate), intra-vesical Botox injection, neuromodulation, and aggressive therapeutic options such as cystectomy. (7)

Being one of the medications used for the treatment of PBPS, PPS is a polysaccharide, and an analogue of the glycosaminoglycan (GAG) layer which protects the bladder epithelium from the toxic components of the urine (8). It was used as an anticoagulant in 1950s due to its thrombolytic activity (9,10). Oral PPS use for the treatment of PBPS was approved by FDA in 1996 (11). To date, it remains to be only oral medication approved for the treatment of PBPS (12). In the United States, approximately 490.000 boxes of PPS were prescribed in 2008 and approximately 450.000 boxes in 2012 (13). These data show how widespread the PPS use is and the level of demand.

Upon this widespread use of oral PPS, its side effects started to draw attention as much as its efficacy. In addition to its systemic side effects, it is thought to have ophthalmologic side effects. Ophthalmologic side effects were first described in 2018 in a series of 6 cases by Pearce et al. Signs of maculopathy causing reading disability and difficulty with dark adaptation have been reported after chronic exposure to PPS in patients diagnosed with PBPS. (14) Controversial results have been observed in the foreign clinical studies on the correlation between PPS use and maculopathy. (15,16) However, to the best of our knowledge, there is no local study on this topic in our country. The present study aimed to assess the correlation between PPS use and pigmentary maculopathy in patients with PBPS.

## Material and Methods

Upon Tekirdağ Namık Kemal University ethics committee approval (Protocol no: 2021.20.01.20), patients diagnosed with PBPS and who received regular oral PPS treatment for at least 12 months were retrospectively included into the study. For every patient diagnosed with PBPS, conditions which may also cause these symptoms (Uro-gynecological cancer, urogenital tract infections, upper urinary tract stone diseases, bladder dysfunction, psychiatric disorders etc.) have been ruled out. All PBPS patients underwent cystoscopic assessment for both subgroup determination and malignancy exclusion. The present study included PBPS patients who were followed in a single center, were in the urinary and non-ulcerative organ-specific phenotype group, and used PPS between 2010 and 2020. In our clinic, PBPS patients are being followed by a multidisciplinary team (by a council consisting of psychiatry, physical therapy and rehabilitation, obstetrics and gynecology, and urology departments). The patients' phenotypes are determined in detail in this council. Upon phenotype assessment, PPS was only initiated to the patients with urinary and non-ulcerative organ-specific phenotype; it was not initiated to the patients in other phenotype groups as the possibility of these patients benefiting from PPS is low. Patients with history of degenerative maculopathy or history of conditions predisposing to maculopathy (age-related macular degeneration, central serous chorioretinopathy, retinal dystrophy, epiretinal membrane, chronic exposure to hydroxychloroquine etc.), who are younger than 18 years, whose pentosan polysulfate sodium dose is less than 100 g, patients with irregular medication use and follow-ups, and patients with a follow-up period less than 12 months were excluded from the study. Moreover, patients with hypertension, chronic vascular diseases and diabetes mellitus predisposing to maculopathy were excluded from the study to avoid possible misdirection. Demographic characteristics, duration of PPS use and total PPS dose of all patients were obtained from the medical records. Patients who were found to be eligible for the study were called to the hospital, informed about the study and referred to the ophthalmology clinic after written informed consent was obtained. Patients who did not want to participate in the study or did not return for eye examination were excluded from the study. Figure 1 shows the patients' study inclusion algorithm.

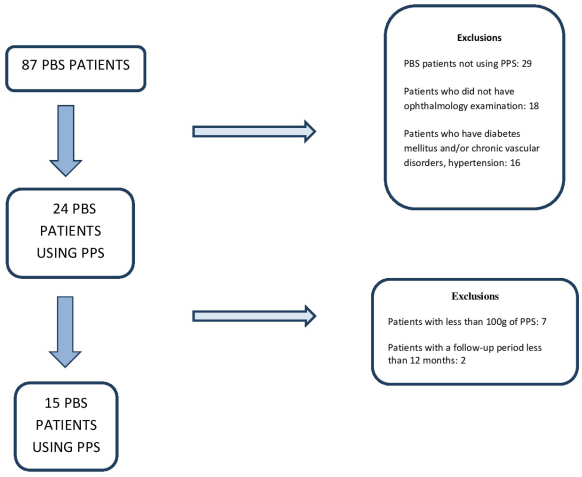


**Figure 1**:
Primary bladder pain syndrome patients using pentosan polysulfate sodium.

All patients who accepted to undergo eye examination were assessed by the same ophthalmologist. Best-corrected visual acuity assessment using Snellen chart, anterior segment and fundus examination using slit lamp biomicroscopy, and intraocular pressure measurement were performed in all patients. Color vision test (Ishihara test), posterior segment optical coherence tomography (Carl Zeiss Meditec, Dublin, CA, USA) examination and 10-2 visual field test (Humphrey Visual Field Analyzer II-i, Carl Zeiss Meditec, Inc) were performed, and color photos and autofluorescence images of fundus (Zeiss Visupac FF450; Carl Zeiss) were taken. (Figure 2) Best-corrected visual acuity, color vision results, macular, choroidal and mean retinal nerve fiber thicknesses, mean deviation of the visual field and fundus findings obtained from the work-up and examinations were recorded.

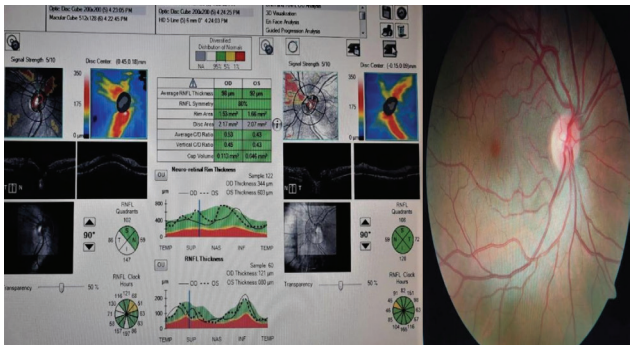

**Figure 2**:
Optic nerve analysis and fundus autofluorescence image

### Statistical Analysis

Statistical analysis of the data was performed using SPSS 23.0 (IBM Corp., Armonk, NY, USA) statistics software. Frequency, rate, mean and standard deviation values were used for the descriptive statistics of the data. The distribution and normality assumption of the data was assessed using Kolmogorov-Smirnov test. Based on the distribution pattern of the data, Student's t test and Mann-Whitney U test were used for the pairwise comparisons of the independent quantitative data.

## Results

Out of 15 patients included into the study, 4 (37.5%) were male and 11 (73.3%) were female. The mean age of the patients was 53.3±11.2 years. During their follow-up, the duration of oral PPS use was found to be 33.01±10.59 months, cumulative oral PPS dose to be 216.02±97.63 g and duration of diagnosis to be 66.64±39.37 months. Table 1 shows the PPS use characteristics of the patients in detail.

As one patient had one prosthetic eye, 29 eye units were assessed in a total of 15 patients. The best-corrected visual acuity of the patients was detected to be 0.98. In the anterior segment examination, senile cataract was observed in both eyes of 1 (6.7%) patient, and anterior segment examination was usual in all the other patients. Intraocular pressure values were normal in all patients, and there was no sign of glaucoma in any of the patients. No pathology was detected in optic nerve head and macula assessment. Color vision was normal in all patients. The mean central macular thickness of the patients was measured to be 254.55±33.11 µm with mean choroidal thickness being measured to be 261.82±34.22 µm. The patients had normal visual field tests with mean deviation being detected to be -1.89 ±-1.25 dB. All patients had normal fundus autofluorescence images with mean retinal nerve fiber thickness being measured to be 98.1±17.62 µm. The ocular results of 8 patients with a mean cumulative dose less than 216 g and 7 patients with a mean cumulative dose more than 216 g were assessed within their own subgroup. Macular and choroidal thicknesses, mean optic nerve thicknesses and visual field findings of the patients were compared within their own subgroups. (Table 2) Patients with a total duration of use less than 216 g had macular and choroidal thicknesses of 262.12 ±18.08 µm and 251.87±34.19 µm, respectively. Patients with a total

**Table 1** Demographic characteristics and PPS use data of the patients

| | |
|---|---|
| **Age, years** | 53.36 ± 11.22 |
| **Daily PPS use, mg** | 242.86 ± 51.35 |
| **Cumulative PPS dose, g** | 216.02 ± 97.63 |
| **Duration of Use, months** | 33.01 ± 10.59 |
| **Duration of PBPS diagnosis, months** | 62.64 ± 39.37 |

PPS: Pentosan polysulfate sodium , PBPS: Primary bladder pain syndrome,

**Table 2** The relationship between the patients' dose and ocular findings

| | Cumulative PPS dose ≤ 216 g | Cumulative PPS dose ≥ 216 g | p value | Exposure time ≤ 33 months | Exposure time ≥ 33 months | p value |
|---|---|---|---|---|---|---|
| Macular thickness (µm) | 262.12 ± 18.08 | 245.23 ± 44.48 | 0.176 | 260.71 ± 21.84 | 251.92 ± 46.63 | 0.558 |
| Choroidal thickness (µm) | 251.87 ± 34.19 | 274.07 ± 31.25 | 0.082 | 242.51 ± 36.69 | 263.14 ± 31.14 | 0.671 |
| Visual field (dB) | -2.02 ± 1.21 | -1.78 ± 1.33 | 0.054 | -1.83 ± 1.01 | -2.24 ± 0.81 | 0.394 |
| Mean retinal nerve fiber thickness (µm) | 93.68 ± 9.04 | 92.38 ± 24.92 | 0.847 | 97.21 ± 21.74 | 94.91 ± 28.37 | 0.811 |

PPS: Pentosan polysulfate sodium

duration of use more than 216 g had macular and choroidal thicknesses of 245.23 ±44.48 µm and 274.07±31.25 µm, respectively. While there are numerical differences between the values, they did not reach a clinical or statistical significance.

## Discussion

Clinical classification was first developed by Nickel et al. (17). The patients were classified in 6 phenotypes (UPOINT) by their symptoms (urinary, psycho-social, organ-specific, infectious, neurological/systemic, muscle tenderness). This classification explains that there is no standard therapy for PBPS; the treatment should be tailored to each patient by assessing them individually. Moreover, the treatment even varies within the subgroup itself; for example, while therapeutic options such as chondroitin sulfate, PPS, intravesical Botox injection were used in patients with predominant organ-specific symptoms without Hunner ulcer, endoscopic methods are recommended for cases with Hunner ulcer. (18) Patients included in our study were patients in the urinary and/or organ-specific phenotypic subgroup recommended to use PPS who do not have Hunner ulcer in the endoscopic examination. PBPS reflects a highly heterogeneous patient population with its subgroups and phenotypic characteristics. Therefore, it is difficult to perform a specific study by forming a homogeneous group of PBPS patients. The PBPS patients in our study were only patients in the urinary and/or organ-specific subgroup who do not have Hunner ulcer. We believe that this is the main difference from the other PBPS studies.

As pentosan polysulfate sodium is a close analogue of GAG, it has been shown to protect the bladder epithelium from the irritative effect of the urine by binding to the bladder epithelium. As the patients use PPS for years; discussions were made on the efficacy as well as the side effects of the medication. When the recent studies are reviewed, it was observed that there are controversial results on the correlation between the long-term PPS use and maculopathy. In their study, Jain et al. reported that the risk of maculopathy is increased by 5.4% due to PPS use after 7 years of follow-up; in their study, Vora et al. found this rate to be 23.4%. (16,19). On the other hand, in their study, Ludwig et al. reported a maculopathy rate of 2.3% after 5 years of follow-up in patients using PPS and stated there is not a strong correlation between them. (15) Consistent with the results of the study by Ludwig et al., no sign of maculopathy was detected in any of the patients with long-term PPS use in our study.

In the present study, the mean duration of PPS exposure was detected to be 33 months. It is known that the duration of chronic exposure to PPS was short, 10-13 months in the study by Jain et al. To the best of our knowledge, our study is the first publication on this topic in our country, therefore, we believe that it is important as it helps generate local data and blazed the trail for further studies.

A total of 15 patients were evaluated in our study; while this sample size appears to be relatively low, the total number of patients was reduced due to the incidence of PBPS and the fact that the study only included PBPS patients who have phenotypes requiring PPS use. Furthermore, when the fact that patients with hypertension, diabetes mellitus or chronic vascular diseases which may cause maculopathy were excluded from the study to avoid misdirection is considered, the number of cases decreases further; therefore, since we used a completely homogeneous group, we believe that a sample size of 15 patients is sufficient. While a correlation was detected between PPS use and maculopathy in the studies by Jain et al. and Vora et al., they did not exclude patients with diabetes mellitus, hypertension and other chronic

vascular diseases. In line with this information, it is highly difficult to say whether the reason for the maculopathy detected in the patients is the chronic diseases or the cumulative effect of PPS. (16, 19) One of the most important advantages of the present study is the formation of a homogeneous group by performing phenotype and subgroup analysis, and excluding patients with comorbidities.

In their study, Vora et al. detected a maculopathy rate of 23.1% after a PPS exposure of 500 g and above, 30.0% after a PPS exposure of 500-1000 g and 41.7% after a PPS exposure above 1500 g. (19) In their study, William et al. found a maculopathy rate of 16% despite a total cumulative dose of 2263 g. (14) These varying findings in the literature show that the results on the correlation between PPS use and maculopathy are controversial. It would be expected that the more the cumulative dose to which the patients are exposed the more the incidence is increased.

There are publications reporting that retinal toxicity findings progress upon pentosan polysulfate sodium use even after the discontinuation of the medication. The reason for the development of the signs of delayed toxicity was considered to be the metabolization of PPS by desulfurization in the liver and the spleen, and in part, by depolymerization in the kidney. It is believed that chronic exposure to PPS over the years causes saturation in the depolymerization and desulfurization pathways. While no correlation was found between the PPS use and maculopathy in our study, the patients should be informed about the possibility of delayed retinal toxicity. (20,21).

Our study had several limitations including retrospective design and limited number of patients, and several strengths including having a group refined from the comorbidities which may predispose the patients to maculopathy, and a mean follow-up period of 33 months. While the fact that the total cumulative PPS dose was lower than the dose used in international studies is considered as a disadvantage, to the best of our knowledge, we believe that this study has the advantage of being the first publication in our country on this topic.

## Conclusion

Used for the treatment of patients diagnosed with PBPS, PPS is an effective method of treatment in urinary and non-ulcerative organ-specific phenotypes. While the present study did not detect any correlation between PPS use and maculopathy, the patients should be informed about the possibility of delayed toxicity. Larger, multi-center, prospective studies are needed to assess the correlation between chronic exposure to PPS and maculopathy more clearly.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Ethical Approval

The study was conducted in line with the principles of the Helsinki Declaration. Ethical Approval was obtained from Tekirdağ Namık Kemal University Non-Invasive Clinical Research Ethics Committee (Date: 26.01.2021, No: 2021.20.01.20).

### Consent to Participate and Publish

Written informed consent to participate and publish was obtained from all individual participants included in the study.

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