

Development of Hyperalgesia in Patients Treated with Autologous Platelet Rich Plasma Due to Androgenetic Alopecia

Androgenetik Alopesi Tedavisinde Otolog PRP Uygulanan Hastalarda Hiperaleji Gelişimi

Öz

Amaç: Platelet zengin plazmanın (PZP) etkisini trombositlerin alfa granüllerinde bulunan büyüme faktörleri ile yüksek trombosit konsantrasyonuna bağlı olarak gösterdiği düşünülmektedir. Tekrarlayan girişimlerde artan ağrı hissi, PZP'nin hipersensitizasyonla ilişkili hiperalejiye neden olabileceği sorunu gündeme getirmektedir. Literatürde tekrarlayan PZP enjeksiyonunun neden olduğu periferik duyarlılığı bildiren yayın yoktur. Bu çalışmada, androjenik saç kaybı olan PZP hastalarında hipersensitizasyona bağlı hiperalejinin olup olmadığını araştırmayı amaçladık.

Hastalar ve Yöntem: Çalışmaya 2016-2017 yılları arasında androjenetik alopesisi olan 25-35 yaşları arasında 10 erkek hasta dahil edildi. Otolog PZP, frontal ve parietal bölge derisine cm² başına 1 mL enjekte edildi ve enjeksiyon birinci, ikinci ve altıncı ayda tekrarlandı. Hastaların ağrılı uyarılara verdiği cevaplar, tüm enjeksiyonlardan hemen önce ve ilk yılda, değişken olarak Von Frey filamentleri kullanılarak araştırıldı. Her bir ölçümün hiperaleji skorları, iki cerrahın ortalama sonuçları ile belirlendi. Saç kaybı olan hastalar dermoskopi ile değerlendirildi. Birim alandaki saç folikülü sayısı tespit edildi ve hastaların her bir kontrolünde fotoğraf çekildi.

Bulgular: Hastaların yaş ortalaması 29,4 idi. Hastalar hiperaleji açısından değerlendirildiğinde, her PZP uygulamasından sonra, PZP enjeksiyonu öncesi ile karşılaştırıldığında ağrının daha az g stimülasyonu ile hissedildiği gözlemlendi (P < 0.05). Hiperalejinin en yüksek periyodu PZP'den sonraki ilk yıldaydı (P < 0.05). Saç yoğunluğundaki artış, ilk tedaviden sonra 1., 2., 6. ve 12. aylarda % 6,4 , 9,4 , 21 ve 27,6 olarak hesaplandı.

Sonuç: Hastalarda tekrarlayan PZP enjeksiyonları nedeniyle hiperaleji ortaya çıkabilir. Bu hastalarda hiperalejinin gelişimi PZP içeriğindeki büyüme faktörlerine bağlı olabilir. Tekrarlanan PZP enjeksiyonlarından sonra ortaya çıkan hiperalejinin nedenini belirlemek için ileri deneysel ve klinik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Plateletten zengin plasma, hiperaleji, androjenetik saç kaybı, PZP

Abstract

Aim: Platelet-rich plasma (PRP) is thought to exert its effect through the growth factors present in the alpha granules of the platelets, depending on its high platelet concentration. The increasing feeling of pain in recurrent attempts raises the question that PRP may cause hyperalgesia associated with hypersensitization. There is no publication in the literature reporting peripheral sensitization caused by any recurrent injection of PRP. In this study, we aimed to investigate whether hyperalgesia occurs due to hypersensitization in PRP patients with androgenetic alopecia.

Patients and Methods: Between 2016 and 2017, 10 male patients aged 25-35 years who had androgenetic alopecia were included in the study. Autologous PRP was injected intradermally as 1 mL per cm² in the diseased frontal and parietal area of scalp, and then the injection was repeated at the first, second and sixth months. Patients' responses to painful stimulus were investigated immediately before all injections and at the first year using Von Frey filaments in variable. Hyperalgesia scores of each measurement were determined by averaging results of the two surgeons. Patients who had hair loss were evaluated with dermoscopy. The number of hair follicles per unit area was detected and the patients' photographs were taken at each control.

Results: The mean age of the participants was 29.4 years. When patients were evaluated for hyperalgesia, it was observed that after each PRP application, pain was felt with less amount of g stimulation compared to before PRP injection (p < 0.05). The highest period of hyperalgesia was in the first year after PRP (P < 0.05). The increase in hair density was calculated as 6.4, 9.4, 21, and 27.6% at 1st, 2nd, 6th, and 12th months after the first treatment.

Conclusion: We determined that hyperalgesia may occur in patients because of repeated PRP injections. The development of hyperalgesia in these patients may be due to growth factors in the PRP content. Further experimental and clinical studies are needed to determine the cause of hyperalgesia occurring after repeated PRP injections.

Keywords: Platelet-rich plasma, hyperalgesia, androgenetic alopecia, PRP

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INTRODUCTION

Clinical use of platelet-rich plasma (PRP) is

increasing day by day. Plastic surgeons implement PRP applications for both functional and aesthetic

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purposes. PRP, which is becoming increasingly popular among minimally invasive applications today, is applied alone or in combination with other aesthetic applications in such as facial rejuvenation, hair loss (1). PRP is thought to exerts its effect through the growth factors present in the alpha granules of the platelets, depending on its high platelet concentration (2). PRP applications are usually applied repeatedly in order to benefit from the positive effects of PRP (3). Patients' complaints of pain during and after these applications are a condition that is faced by treating physicians, and sometimes make the treatment difficult. The increasing feeling of pain in these recurrent attempts raises the question that PRP may cause hyperalgesia associated with hypersensitization. There is no publication in the literature reporting peripheral sensitization caused by any recurrent injection of PRP.

In this study, we aimed to investigate whether hyperalgesia occurs due to hypersensitization in PRP patients with androgenetic hair loss.

PATIENTS AND METHODS

Between 2016 and 2017, 10 male patients aged 25-35 years who had hair loss were included in the study. Patients with chronic disease and deficiencies of androgenic and thyroid hormone, B12 vitamin and Fe were excluded from the study. Autologous PRP was injected intradermally as 1 mL per cm² in the diseased frontal and parietal area of scalp, and then the injection was repeated at the first, second and sixth months. Patients' responses to painful stimulus were investigated immediately before all injections and at the first year using Von Frey filaments (Table. 1) in variable. Measurements were made on the fixed area. This area was defined as 1 cm² at the junction of the imaginary line drawn in the midline face with the line joining the two tragus lines of the patients (Figure 1). PRP application and investigation of hyperalgesia were performed by two separate plastic surgeons as double blind. Hyperalgesia was investigated with the smallest 0.008 g, and the largest 300 g 20 Von Frey needles. Hyperalgesia scores of each measurement were determined by averaging results of the two surgeons. Patients who had hair loss were evaluated with dermoscopy. The number of hair follicles per unit area was detected and the patients' photographs were taken at each control.

Preparing the PRP

Four pieces of the True Cell 10 mL PRP kit were used

Table 1. The size and power scale of the von frey filaments.

Size	Force (g)
1,65	0,008
2,36	0,02
2,44	0,04
2,83	0,07
3,22	0,16
3,61	0,4
3,84	0,6
4,08	1
4,17	1,4
4,31	2
4,56	4
4,74	6
4,93	8
5,07	10
5,18	15
5,46	26
5,88	60
6,1	100
6,45	180
6,65	300

for preparing the autologous PRP. A 40-mL sample of blood was taken from each patient and transferred to the PRP kits. And then, it was centrifuged at 3000 rpm for 10 min. At the end of this procedure, an average of 4-5 mL of PRP was obtained for each patient.

Statistical Analysis

The statistical significance of the differences between the mean values was analyzed using SPSS 24.0 (USA) statistical software. Repeated measures for t- test adjusted sample test were used to compare



Figure 1. Hyperalgesia measuring area (marked with red box)

the occurring hyperalgesia at the pre-and post-PRP treatment. The level of significance was accepted as < 0.05.

RESULTS

The mean age of the participants was 29.4 years. Ten patients were followed up for 1 year. The mean pre-determined area of patients (before initial application) was calculated as 0.84 g (min.0.6 -max.1g). The mean value was found as 0.5 g (min.0.4 -max.0.6 g) at the first month (before the second application), 0.304 g (min.0.16 -max.0.4 g) at the second month, and 0.172 g (min.0.07 -max.0.4 g) at the 6th month (before the fourth application). The mean value in the first year was calculated as 0.0284 g (min.0.008-max0.04.g) (Figure 2). When patients were evaluated for hyperalgesia, it was observed that after each PRP application, pain was felt with less amount of g stimulation compared to before PRP injection. (p <0.05) The highest period of hyperalgesia was in the first year after PRP (P <0.05). On the other hand, patients who underwent PRP because of hair loss were evaluated with dermoscopy. An increase was detected in the number of hair follicles in unit area (cm²) (Figure 3).

The increase in hair density was calculated as 6.4, 9.4, 21, and 27,6% at 1st, 2nd, 6th, and 12th months after the first treatment. (Figure 4)

DISCUSSION

After a painful stimulus in tissue-damaged area, inflammation is induced by secretion of substances such as substance P, neurokinin A, and gene related peptide of calcitonin. Peripheral sensitization occurs because of the stimulating high-threshold nociceptors. Low-level mechanical stimulus begin to

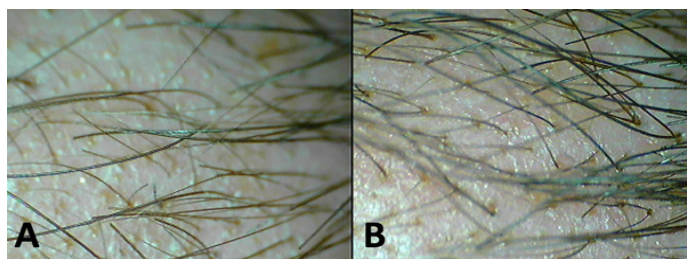


Figure 3. (A) Preoperative and (B) postoperative appearance of a patient in dermatoscope.

be perceived as painful (hyperalgesia). The medical term hyperalgesia refers to hypersensitivity against pain (4). Hyperalgesia, which is characterized by the occurring of sensitization to normal pain values, is closely related to inflammation and neuropathic pain (5). A number of mechanisms of sensitization have been identified in the literature, such as tissue damage, and increased inflammatory mediators in the interstitial area (6-7).

A large number of protein and growth factors are found in alpha granules contained within platelets. Growth factors are involved in pathways such as inflammation, angiogenesis, atherosclerosis and wound healing by stimulating other cells, especially mesenchymal stem cells, by binding to the resulting transmembrane proteins associated with coagulation inductors (8). Contrary to the mechanisms of sensitization which are caused by tissue damage and inflammatory mediators, it is not possible to explain the development of sensitization by tissue damage and inflammation in PRP treatments used for tissue repair in this direction. Growth factors in PRP may be

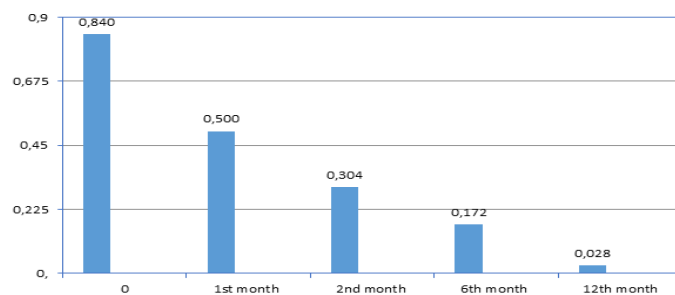


Figure 2. The mean hyperalgesia scores of patients at the pre and post-PRP treatment.

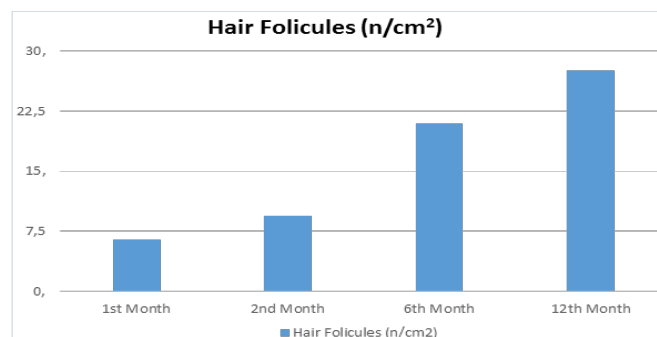


Figure 4. The mean number of hair follicles in unit area at the pre and post-PRP treatment.

thought to have a pain threshold decreasing effect in neural structures involved in pain pathways.

In our study, we observed that hyperalgesia occurred because of the recurrent injections of PRP. The reason for this may be that PRP treatments lead to an increase in number and sensitivity of the nociceptors and an increase in growth factors such as NGF, PDGF, and VEGF in the tissue (9). However, PRP has been used especially in soft tissues due to the antiinflammatory effect of PRP. In our study and the studies in the literature, it has been thought that inflammatory mediators and growth factors could produce hyperalgesia by peripheral sensitization of tissue by stimulating nociceptors in the tissue (10). No biopsies were taken from the patients. Despite the disadvantage that there was no control group in the study, based on the results obtained from the study, we believe that PRP, which can be used in patients with diseases such as diabetic foot, peripheral neuropathy, may increase sensitization of the disease, affecting diseases positively.

It was reported that PRP treatment is effective for androgenetic alopecia. When the patients were evaluated in terms of hair loss treatment, the increase in hair density was calculated as 6,4/cm² at the 1st month, 9,4 at the 2nd month, 21 and 27,6 at the 12th month after the first treatment. The values were in accordance with the literature.

In the literature, occurring of hyperalgesia with PRP injections has not yet been reported. This study is the first in the literature to report hyperalgesia with PRP injections.

In conclusion, we determined that hyperalgesia may occur in patients because of repeated PRP injections. The development of hyperalgesia in these patients may be due to growth factors in the PRP content. Further experimental and clinical studies are needed to determine the cause of hyperalgesia occurring after repeated PRP injections.

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