Efficacy of High-Dose Bevacizumab Treatment in the Management of Epistaxis in Cases with Osler-Weber-Rendu Syndrome

Erdem Eren[1], Mustafa Koray Balcı[1], Akif İşlek[2], Şerife Solmaz Medeni[3], Kamran Hasanlı[1]

[1]Department of Otorhinolaryngology, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey
[2]Department of Otorhinolaryngology, Nusaybin State Hospital, Mardin, Turkey
[3]Department of Hematology, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Turkey

Abstract

Objective: This study presents the experience in epistaxis management in cases with Osler-Weber-Rendu syndrome (OWRS) and the outcomes of intravenous bevacizumab treatment in selected cases.

Material and methods: The records of patients diagnosed with OWRS who underwent medical and/or surgical treatment in the Otorhinolaryngology department of İzmir Katip Çelebi University Atatürk Training and Research Hospital between 2004 and 2018 were retrospectively reviewed. Consequently, 10 patients diagnosed with OWRS according to Curaçao's criteria were included in the study.

Results: The mean epistaxis severity score (ESS) of the patients were 5.42±1.07 and 3.86±0.89 at first admission and after 3 months of follow-up, respectively. Moreover, four patients (40%) were evaluated for intravenous bevacizumab treatment after the initial treatment and/or surgery. Three patients underwent a high dose (5 mg/kg every 2 weeks for six times) of bevacizumab treatment, whereas one patient underwent a low dose (0.125 mg/kg every 2 weeks for six times) followed by a high dose of bevacizumab treatment. A decrease in ESS was observed in all cases after the treatment.

Conclusion: Bevacizumab may be a promising agent for patients with refractory epistaxis. Currently, it is not approved for the treatment of Osler-Weber-Rendu syndrome and a multidisciplinary approach can be considered for off-label use.

Keywords: Osler-Weber-Rendu syndrome, epistaxis, bevacizumab

INTRODUCTION

Osler-Weber-Rendu syndrome (OWRS), also known as hereditary hemorrhagic telangiectasia (HHT), is a chronic debilitating disease that causes recalcitrant epistaxis. OWRS is diagnosed because of the presence of at least three of Curaçao's four criteria: epistaxis, cutaneomucosal telangiectasias, familial history, and visceral arteriovenous deformities. Clinical diagnosis is suspected or possible with two criteria, and at least three criteria are required for the definite diagnosis (1). Most of the patients suffer from epistaxis, which varies from occasional minor bleeding to life-threatening massive bleedings.

The mechanical stress triggered by turbulent flow is considered to be responsible for epistaxis. The therapy for epistaxis in OWRS varies according to the bleeding severity. Thus, nasal mucosal care, nasal packing, medical treatments, and surgical interventions can be utilized according to the case (2).

Vascular endothelial growth factor (VEGF) is a signal protein that stimulates angiogenesis and vasculogenesis (3). VEGF's normal function is to generate vessels during embryonic development or after injuries. It also helps to create collateral circulation to bypass obstructed vessels. In addition, VEGF can contribute to the pathologic processes where solid malignant tumors that can express VEGF can rapidly grow and metastasize (3). Moreover, bevacizumab is a recombinant, humanized monoclonal antibody that binds to and inhibits VEGF, thereby preventing endothelial cell proliferation and angiogenesis. It is mostly used in oncology and ophthalmology practice, especially for clinical entities that involve pathologic new vessel growth. Bevacizumab is an intriguing treatment option for HHT-associated epistaxis (2).

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Address for Correspondence: Mustafa Koray Balcı

E-mail: m.koray.balci@gmail.com

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Table 1. Summary of patients who underwent i.v. bevacizumab treatment

No	Age	Sex	Admission symptom	Curaçao's criteria	ESS at admission	ESS after surgery	Dose of bevacizumab	ESS before bevacizumab	ESS after bevacizumab	Surgical treatments
1	51	M	Epistaxis	3	8.33	7.14	Low dose followed by high dose	7.38	3.28	TC, SPAL, SDP
2	55	M	Epistaxis	3	5.42	3.98	High	3.83	2.14	TC, SDP
3	60	M	Epistaxis	3	7.15	4.66	High	4.35	2.58	TC, SPAL
4	74	F	Melena, Epistaxis	3	5.16	4.95	High	4.76	2.39	TC

ESS: normalized epistaxis severity score; TC: telangiectatic cauterization; SPAL: sphenopalatine artery ligation; SDP: septodermoplasty

This study aimed to present the experience in epistaxis management in OWRS cases and to present the outcomes of intravenous bevacizumab treatment in selected cases.

MATERIAL AND METHODS

The records of patients diagnosed with OWRS who underwent medical and/or surgical treatment in our clinic between 2004 and 2018 were retrospectively reviewed. Patients were diagnosed according to Curaçao's criteria. Age, gender, medical history, symptoms at initial diagnosis, the most common symptoms after the diagnosis, symptoms regarding head and neck, epistaxis severity score (ESS) (4), and treatment methods were evaluated for 10 patients who met the criteria. ESS scores were calculated and recorded at the first admission after the diagnosis. The study was approved by the Instutitional Review Board of İzmir Katip Çelebi University (Approval Date: December 10, 2018; Approval Number: 2018-0608).

Microsoft Excel 2010 (Microsoft, Redmond, WA, USA) was used for statistical analysis of data.

RESULTS

Ten patients were diagnosed with OWRS according to Curaçao's criteria. Although all patients suffered from recurrent epistaxis, only seven patients presented with epistaxis. The mean age of the patients was 58.3±12.3. Eight patients were males (80%) and two were females (20%).

The mean ESS of the patients was 5.42±1.07 and 3.86±0.89 at the first admission and after 3 months of follow-up, respectively. All patients were treated with standard cotton pads impregnated with lidocaine, adrenaline, and tranexamic acid as the first step of treatment. Silver nitrate cauterization was performed for all telangiectatic vessels, and an absorbable hemostatic gelatin sponge (Spongostan, Johnson & Johnson; New Brunswick, NJ, USA) or Merocel (Medtronic Inc.; Minneapolis, MN, USA) packing was placed in both nasal passages. Merocel packings were removed after 48 h. Patients were treated with tranexamic acid (750 mg/day), cefuroxime axetil (1,500 mg/day), and pheniramine (45.5 mg/day) during hospitalization. The first-choice agent for pain management was paracetamol (2,000 mg max/day). However, nonsteroid anti-inflammatory drugs were administrated for patients who did not respond to paracetamol treatment. Surgical treatment was considered for patients who did not respond to initial treatment.

After the initial treatment and/or surgery, four patients (40%) with resistant epistaxis or uncontrolled gastrointestinal (GIS) bleeding were evaluated for intravenous bevacizumab treatment. On the one hand, a 51-year-old male with resistant epistaxis underwent telangiectatic vessel cauterization, bilateral endoscopic sphenopalatine artery ligation, and bilateral septodermoplasty. Refractory epistaxis continued after the surgery. The patient was administered a low dose of intravenous (i.v.) bevacizumab treatment (0.125 mg/kg, six times every 2 weeks). The decrease in epistaxis was only for 1 year. Consequently, the patient consulted at the hematology clinic and a high dose of i.v. bevacizumab treatment was administered (5 mg/kg, six times every 2 weeks). On the other hand, a 74-year-old female complaining of melena and epistaxis underwent telangiectatic vessel cauterization and was admitted to the hematology clinic for a high dose of i.v. bevacizumab treatment for uncontrolled GIS bleeding. Similarly, the other two patients also underwent a high dose of i.v. bevacizumab treatment. Consequently, ESS decreased after the treatment in both cases. Medical data of patients who underwent i.v. bevacizumab treatment is summarized in Table 1. No side-effects were encountered during the treatment.

DISCUSSION

Recurrent epistaxis is the most important and common symptom of OWRS (5). However, the major complaint was epistaxis for only seven (70%) patients although all patients in this study suffered from epistaxis. OWRS, which is an inherited autosomal dominantly, has a frequency of approximately 1:5,000-1:8,000 (6). The penetrance of genes transmitting the syndrome reach 100% at 40 years old (6). Nasal bleeding occurs before 21 years in 90% of patients (7). The mean age of the patients in this study was 58.3±12.3 years, and 90% of the patients were diagnosed at over 40 years of age. This information reveals the importance of anamnesis and family history in the diagnosis of OWRS in patients presenting with epistaxis.

Several modalities are present for the treatment of epistaxis in OWRD. Different options can be selected depending on symptom severity. Nasal mucosa treatment is the first and most important step. Consequently, protecting the nasal mucosa from drying out is the best way of preventing epistaxis. This can be achieved by daily application of creams, oils, and hygroscopic sprays (2).

Tranexamic acid is an antifibrinolytic agent that can be used orally. It is currently the only medication approved for OWRS treatment (8). Interventional procedures like chemical cauterization with silver nitrate, bipolar electrocauterization, bipolar diathermy, argon plasma coagulation, coblation, and laser treatment can reduce the severity and frequency of epistaxis (9). However, nasal packings can be used in an emergency scenario (2).

Septodermoplasty is a surgical procedure that involves the resection of the diseased mucosa and split-thickness graft replacement to the resected site. Septodermoplasty (SDP) was performed on two patients in this

study. The main drawback of SDP is that its effectiveness decreases over time. Consequently, a recent French guideline does not recommend SDP and advises Young's procedure as the last step (7). However, patients are reluctant to undergo Young's procedure as per experience in this study.

A promising treatment regimen in HHT is bevacizumab, which is a VEGF inhibitor. The outcomes of submucosal, topical, or i.v. bevacizumab applications are available in the literature (10). Riss et al. (11) reported a decrease in ESS scores from 3.9±1.9 to 2.9±1.4 after submucosal bevacizumab application in their prospective randomized controlled trials. The authors reported no significant difference when compared with the control group (p=0.34). In addition, a significant reduction in epistaxis duration was reported in another study that included bevacizumab injections for epistaxis control in OWRS after a follow-up of 6 months (12). The mean ESS decreased from 7.19 to 5.86 in patients who undergo i.v. bevacizumab treatment in the current study. In the study of Thompson et al. (13), six patients were followed with a single low dose of i.v. bevacizumab per month. The mean ESS value decreased from 7.2±2.1 to 3.3±1.9 (p=0.004) when the six doses were completed (13). Likewise, one of the patients was also treated with a low dose of i.v. bevacizumab but the decrease in the epistaxis severity was only for 1 year. A high dose of i.v. bevacizumab application resulted in a longer epistaxis control in four patients. Thus, a high dose of i.v. bevacizumab treatment may be a convenient option for patients with refractory epistaxis. However, the main handicap of bevacizumab treatment is that it is not approved by the Food and Drug Administration for OWRS treatment. Therefore, special permission is needed for off-label use. In addition, Halderman et al. (10) concluded that this expensive treatment protocol should be selected considering the profit-loss ratio in patients with high ESS.

This study has certain limitations. Only 10 cases were presented, and only four of them were treated with bevacizumab. These four cases also underwent interventional procedures. Considering the rarity of the disease and various treatment modalities, reaching a certain conclusion about the efficacy of bevacizumab treatment is difficult.

CONCLUSION

Osler-Weber-Rendu syndrome is a highly debilitating disease that currently does not have a cure. Although medical and surgical treatments are available, no consensus exists on symptom management. However, bevacizumab may be a promising agent for patients with refractory epistaxis. Moreover, it is not currently approved for the treatment of Osler-Weber-Rendu syndrome, and a multidisciplinary approach can be considered for off-label use.

Ethics Committee Approval: Ethics committee approval was received for this study from the Instutitional Review Board of İzmir Katip Çelebi University (Approval Date: December 10, 2018; Approval Number: 2018-0608).

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