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Case Report

Electromagnetic Iontophoresis: A Novel Nonsurgical Method for the Treatment of Dense Vitreous and Retinal Hemorrhages

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Keywords

Electromagnetic iontophoresis · Magnovision · Preretinal hemorrhage · Subretinal hemorrhage · Vitreous hemorrhage

Abstract

Introduction: Vitreous, retinal, and suprochoroidal hemorrhages might develop secondary to trauma, retinal tear or detachment, neovascularization due to ischemic retina. If the clearance of retinal and vitreous hemorrhages can be accelerated, more effective treatments can be planned for the underlying pathology. ***Case Presentations:*** We present 6 different cases with dense vitreous, preretinal, and subretinal hemorrhages due to Valsalva retinopathy, polypoid choroidal vasculopathy, diabetic retinopathy, neovascular age-related macular degeneration, retinitis pigmentosa with vasculitis, and myopic choroidal neovascularization. To accelerate the clearance of these dense intraocular hemorrhages, a novel nonsurgical method of electromagnetic iontophoresis (MagnoVision™) was used together with some appropriate medications in an outpatient setting without any complications or side effects. In all cases, liquefaction of the intraocular hemorrhage began by 5 days and mostly resolved by 10 days. This nonsurgical rapid clearance allowed us to diagnose and evaluate the underlying retinal and choroidal pathologies earlier and to treat them appropriately as early as possible. ***Conclusion:*** Combined use of electromagnetic iontophoresis, subtenon platelet-rich plasma and bevacizumab injection, and oral bromelain can be considered as an effective and safe new treatment method for vitreous and retinal hemorrhages without any need for surgical intervention.

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Introduction

Vitreous, retinal, and suprochoroidal hemorrhages might develop secondary to trauma, intraocular surgery, retinal tear/detachment, retina and optic disc neovascularization due to ischemic retina, different types of choroidal neovascularization, and disruption of a retinal artery microaneurysm [1]. During the syneresis and development of acute posterior vitreous detachment, retinal tears and vitreous hemorrhage occur simultaneously as well [2]. Traumatic hemorrhages are often accompanied by only retinal tears or retinal detachment (RD), and their detection by ultrasound is an indication for urgent pars plana vitrectomy (PPV) [1, 2]. Subretinal hemorrhages are also a condition that requires urgent and proper intervention.

PPV, subretinal tissue plasminogen activator injection, and intraocular gas tamponade are the current approaches used to prevent iron intoxication from subfoveal erythrocytes and to displace the coagulum from the macula [3]. However, intense fibrosis may develop in the subretinal area in this approach, and surgery-related complications reduce the success rates [4]. In vitreous hemorrhages, except in cases of trauma, subretinal hemorrhages, and RD, the patient is usually monitored for spontaneous clearance for 3 months. PPV is usually performed if spontaneous clearance does not occur within this time. This observation period may vary depending on the condition of the other eye, the patient's systemic condition, the density of the hemorrhage, and the surgeon's preference.

Early intervention for hemorrhages using PPV may prevent appropriate surgical planning due to the inability to see preoperative retinal details. Early PPV may also commonly have postoperative complication rates and risks of permanent vision loss due to high inflammatory response [4]. However, late planning of PPV may lead to progression of the underlying pathology and an inadequate treatment approach. For example, vitreous hemorrhage in diabetic retinopathy (DR) may prevent early detection of disc neovascularization, and late intervention may accelerate the progression to neovascular glaucoma or tractional retinal detachment [1–4].

YAG laser hyaloidotomy is currently used for sub-internal limiting membrane (sub-ILM) hemorrhages. However, it has problems such as macular damage or delayed clearance of the resulting vitreous hemorrhage [5]. All disadvantages and possible further complications of current treatment approaches indicate a need for new nonsurgical methods for the early treatment of vitreous and retinal hemorrhages. One possibility is electromagnetic iontophoresis with effective medications.

MagnoVision is a stimulator and iontophoresis device that was specifically designed for retina and optic nerve diseases. It contains 9 coils and generates a 2,000-mG magnetic field with a vibration frequency of 42 Hz, which synchronously stimulates the bulbus, visual pathways, and occipital cortex. These parameters are fixed values by the manufacturer and cannot be changed for patient safety. Each session is applied effectively and safely for 30 min. Electromagnetic iontophoresis and stimulation are applied once a day for 30 min for 10 consecutive days [6–10]. We present 6 different cases that were treated with this method. The application and operating principles of the MagnoVision electromagnetic iontophoresis device are available in the online supplementary video (for all online suppl. material, see https://doi.org/10.1159/000544755).

Case Presentations

Case 1

A 48-year-old female patient being followed for lung issues was referred to our clinic with complaints of sudden vision loss in her right eye following cough attacks the day before. According to the ophthalmological examination, her visual acuity (VA) in the right eye was

"counting fingers from 1 m," and her corrected visual acuity (BCVA) in the left eye was 10/10. The intraocular pressure (IOP) was within normal limits in both eyes. Anterior segment findings were unremarkable.

Fundus examination revealed two separate areas of dense preretinal hemorrhage in the right eye: one covering the entire macular area and the other in the supero-nasal region of the optic disc (Fig. 1a). Optical coherence tomography (OCT) showed dense preretinal sub-ILM hemorrhages (Fig. 1b). Retinal examination of the left eye was normal. Treatment was planned as a combination of citrate for coagulum dispersion, platelet-rich plasma (PRP) containing epithelial growth factor to increase the pump function and phagocytosis rate of the retinal pigment epithelium (RPE), anti-vascular endothelial growth factor (VEGF) (bevacizumab) to prevent new hemorrhages, and electromagnetic iontophoresis (MagnoVision™) for vibration of the iron molecules of the hemoglobin in erythrocytes.

Because of a suspected lung infection, PRP was prepared allogeneically from one of the patient's healthy relatives with the same blood type. Allogeneic PRP was prepared by refrigerating a total of 8 mL of blood taken from the relative into a sterile citrated PRP tube. After centrifuging at +4°C and 2,500 rpm for 8 min, the lower 1/3 of the plasma in the tube was withdrawn into a 2.5-mL injector, totaling 1 mL of PRP, and then 0.5 mL of bevacizumab was added to the same syringe. A total of 1.5 mL of the solution of citrate, exosomes, and anti-VEGF mixture was injected into the subtenon space of the right eye under topical anesthesia.

Immediately after the subtenon injection, the helmet of the MagnoVision device was placed on the patient's head in order to provide electromagnetic stimulation for 30 min. Briefly, after the subtenon injection, 10 daily sessions of MagnoVision were performed. One day after the injection and MagnoVision treatment, we observed that the sub-ILM hemorrhage had completely drained into the vitreous (Fig. 1c, d). After the 10th MagnoVision session, we observed that the vitreous hemorrhage was cleared in front of the macula (Fig. 1e, f). After 10 sessions, the VA of the treated right eye had improved to 0.7. On the first injection day of the treatment plan, the patient was started on bromelain tablets, taken twice daily for 1 month. There is evidence in the ophthalmic literature that the natural enzyme bromelain causes chemical vitreolysis, and we hypothesized that it may provide more elimination of erythrocytes between vitreous fibrils.

Case 2

A 67-year-old female patient was referred to our clinic with a complaint of a sudden decrease in vision in her left eye for 3 days. She had been followed up in another center for 2 years with a diagnosis of polypoid choroidal vasculopathy. A total of 8 doses of intravitreal anti-VEGF injections were applied to the left eye in another center, and the last one had been 1 month prior. She stated that her hypertension had been irregular for the last week, and her sudden decrease in vision began after a severe headache.

According to the ophthalmological examination, her VA was "hand motion" in the left eye, and she had 10/10 BCVA in the right eye. IOPs were within the normal limits in both eyes. Biomicroscopic examination revealed senile nuclear sclerosis in both eyes. Fundus examination indicated mild vitreous hemorrhage and extensive subretinal hemorrhage in the left eye. En face and cross-sectional B scan OCT confirmed these findings (Fig. 2a–c). The appearance of the right fundus was normal.

As a treatment, the patient received a subtenon injection of 1.0 mL of autologous citrated PRP solution + 0.5 mL bevacizumab. MagnoVision was applied for 30 min immediately after the injection, as well as once a day for 9 consecutive days. Bromelain tablets were started orally twice a day. By the 5th session, the vitreous hemorrhage had completely cleared, and the subretinal hemorrhage was greatly reduced (Fig. 2d–f). By the 10th session, the subretinal

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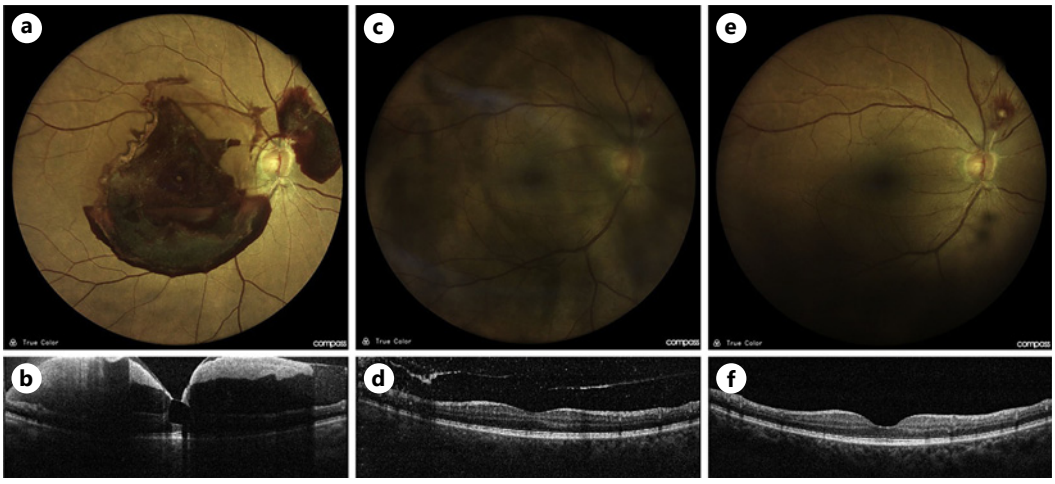

Fig. 1. a Case 1: a 48-year-old female. Color fundus photo of the right eye shows extensive hemorrhage in front of the macula and supero-nasal of the papilla at first presentation. **b** Cross-sectional B scan optical coherence tomography (OCT) shows hemorrhage under the internal limiting membrane (sub-ILM). **c** Color fundus photo shows complete drainage of sub-ILM hemorrhage into the vitreous 1 day after 30 min of MagnoVision application following subtenon citrated platelet-rich plasma + bevacizumab injection. **d** OCT shows that the hemorrhage drains completely from the sub-ILM into the vitreous after the first session of electromagnetic iontophoresis + medication. **e** Color fundus photo shows that the vitreous hemorrhage has been largely cleared, and the macula has been opened by the 10th day of MagnoVision application. **f** OCT shows that the vitreous hemorrhage cleared, and the ILM reattached to the macula without sequelae by the 10th day of MagnoVision application.

hemorrhage had completely cleared, and a disciform scar remained in the macular area (Fig. 2g–i). The VA in the treated left eye was improved to 0.1 BCVA from "hand motion" despite a macular lesion.

Case 3

A 73-year-old female was referred to our clinic complaining of decreased vision in her left eye and black floaters for 10 days. Her medical history included type-2 diabetes mellitus and hypertension for 20 years. However, she stated that she had no regular metabolic control.

According to the ophthalmological examination, her VA was 0.05 in the left eye, and she had 10/10 BCVA in the right eye. IOPs were within the normal limits in both eyes. Biomicroscopic examination revealed pseudophakia in both eyes. Fundus examination showed moderate vitreous hemorrhage and barely visible hard retinal exudates in the left eye (Fig. 3a). There were microaneurysms and mild hard exudates in the right eye.

The patient's left eye was treated with a subtenon injection of 1.0 mL of allogeneic citrated PRP + 0.5 mL of bevacizumab. MagnoVision was applied for 30 min immediately after the injection and once a day for 9 consecutive days. Bromelain tablets were started orally twice a day. By the 10th session, the vitreous hemorrhage had completely cleared, all details of DR could be seen (Fig. 3b), and VA had improved to 0.3 BCVA. Laser photocoagulation was applied to the ischemic areas in the periphery because the patient did not have regular follow-up previously. The patient consulted relevant departments for proper metabolic and systemic control.

Case 4

An 81-year-old male patient came to our clinic with complaints of sudden vision loss and black floaters in his right eye that started 2 days prior. He stated in his medical history that he received anti-VGEF injections 8 years prior with a diagnosis of neovascular age-related

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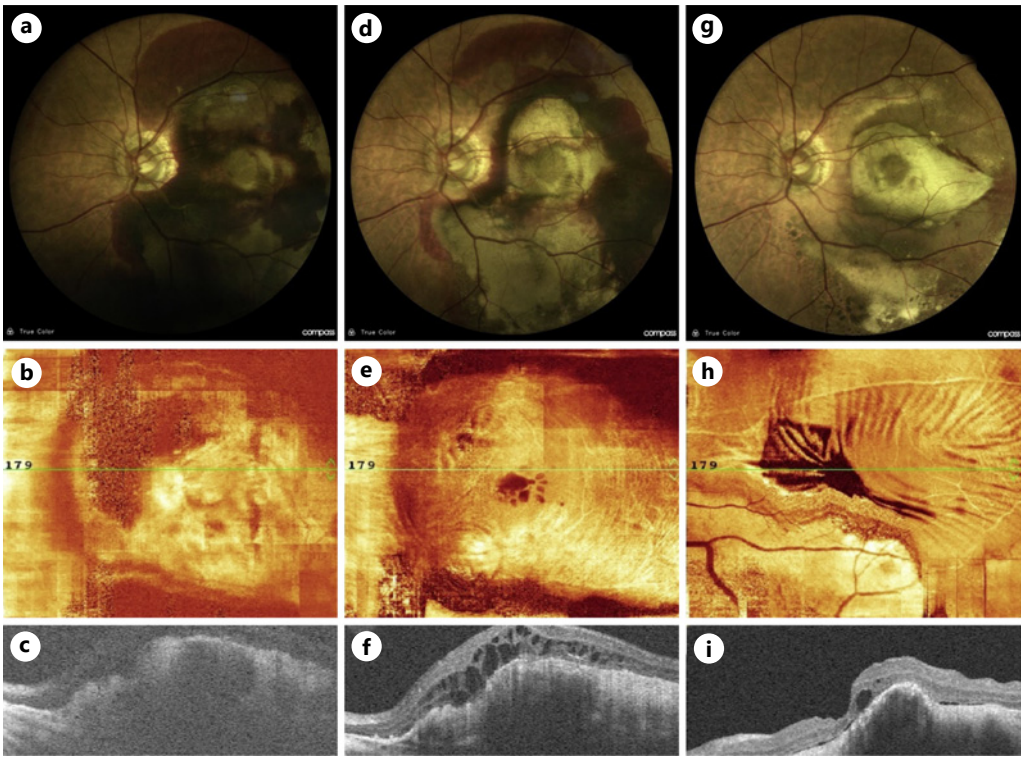

Fig. 2. a Case 2: a 67-year-old female. Color fundus photo of the left eye shows extensive hemorrhage in the macula at first presentation. **b** En face OCT shows that the macular surface is irregular due to hemorrhage. **c** Cross-sectional B scan OCT shows subretinal hemorrhage and mild vitreous hemorrhage. **d–f** After 1 dose of subtenon citrate PRP + bevacizumab injection and 5 sessions of MagnoVision, imaging methods showed that subretinal hemorrhage began to decrease, and vitreous hemorrhage cleared. **g–i** Images show that after 10 sessions of MagnoVision, the subretinal hemorrhage cleared, leaving preserved photoreceptor areas in the nasal macula.

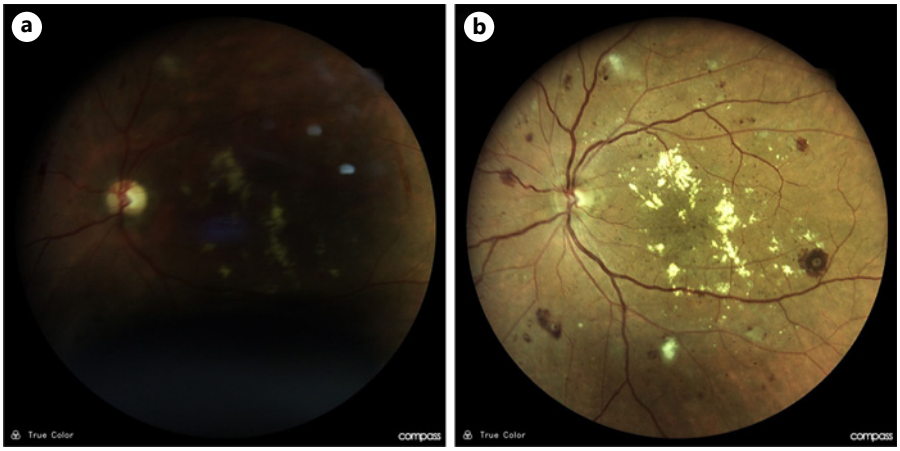

Fig. 3. a Case 3: a 73-year-old female patient. Color fundus photo of the left eye shows moderate vitreous hemorrhage and exudates at first presentation. **b** Color fundus photograph shows that the vitreous hemorrhage cleared after 1 dose of subtenon citrate PRP + bevacizumab injection and 10 sessions of MagnoVision. DR and exudates are clearly seen in the retina.

macular degeneration, and so far, the eye had been stable. He stated that new anticoagulants and medications were started by the cardiology department 1 week prior due to systemic hypertension and arrhythmia.

According to the ophthalmological examination, his VA was 0.05 in the right eye with 6/10 BCVA in the left eye. The IOP was 10 mm Hg in the right and 11 mm Hg in the left. Biomicroscopic examination showed pseudophakia in both eyes. Fundus examination of the right eye displayed blurred macular scarring because of moderate vitreous hemorrhage in the right eye (Fig. 4a). There were drusen and a limited area of atrophy in the macula of the left eye.

The patient's right eye received an injection of 1.0 mL of subtenon autologous citrated PRP + 0.5 mL of bevacizumab. MagnoVision was applied for 30 min immediately after the injection and once a day for 9 consecutive days. Bromelain tablets were started orally twice daily. By the 10th session, the vitreous hemorrhage had mostly cleared, and there was fresh hemorrhage from the peripapillary choroidal neovascularization (Fig. 4b). After the 10th session, the VA in the treated eye improved to 0.3 BCVA. The patient was followed up for detailed fundus examinations and intravitreal injections if required.

Case 5

A 52-year-old male patient came to our clinic with a complaint of sudden vision loss in his left eye that started 1 day prior. His medical history included retinitis pigmentosa for 40 years, some injections in both eyes due to vasoproliferative tumor and vasculitis, and lost light perception in his right eye for 10 years. He stated that he used medications for chronic renal failure and hypertension.

According to the ophthalmological examination, there was no light perception in the right eye and hand motion perception in the left eye. IOPs were within normal limits in both eyes. Biomicroscopic examination showed pseudophakia in both eyes. Fundus examination displayed extensive vitreous hemorrhage in the left eye (Fig. 5a, b). Ultrasound assessment showed that the retina was attached in this eye. Optic atrophy, extensive chorioretinal atrophy, and silicone tamponade were present in the right eye.

The patient received a subtenon injection of 1.0 mL of autologous citrated PRP solution + 0.5 mL of bevacizumab into the left eye. MagnoVision was applied for 30 min immediately after the injection and once daily for 9 days. Bromelain tablets were started orally twice daily. By the 5th session, the vitreous hemorrhage cleared slightly, and the papilla became visible (Fig. 5c, d). After the 10th session, the vitreous hemorrhage cleared almost completely, and retinal details could be observed (Fig. 5e, f). VA improved to 0.2 BCVA in the treated left eye. Telangiectatic vessels were detected in the peripheral retina of the left eye and treated with laser photocoagulation without any difficulty because of resultant vitreous hemorrhage.

Case 6

A 71-year-old male patient had undergone phacoemulsification surgery on his right eye at another clinic 15 days prior with a diagnosis of degenerative myopia and cataract. He developed severe vitreous and suprachoroidal hemorrhage immediately after the surgery and then was referred to our clinic. His medical history included degenerative myopia and Marfan syndrome since childhood. He stated that he had surgery on his left eye at the same center 2 years prior due to lens luxation.

According to the ophthalmological examination, his VA was "hand motion" in the right eye and 1/10 BCVA in the left eye. The IOP was 9 mm Hg in the right eye and 10 mm Hg in the left eye. In the biomicroscopic examination, both eyes were aphakic. Fundus examination showed extensive vitreous hemorrhage in the right eye (Fig. 6a). Ultrasound examination also displayed severe intravitreal and suprachoroidal hemorrhage, and there was extensive chorioretinal atrophy and posterior staphyloma due to degenerative myopia in the left eye.

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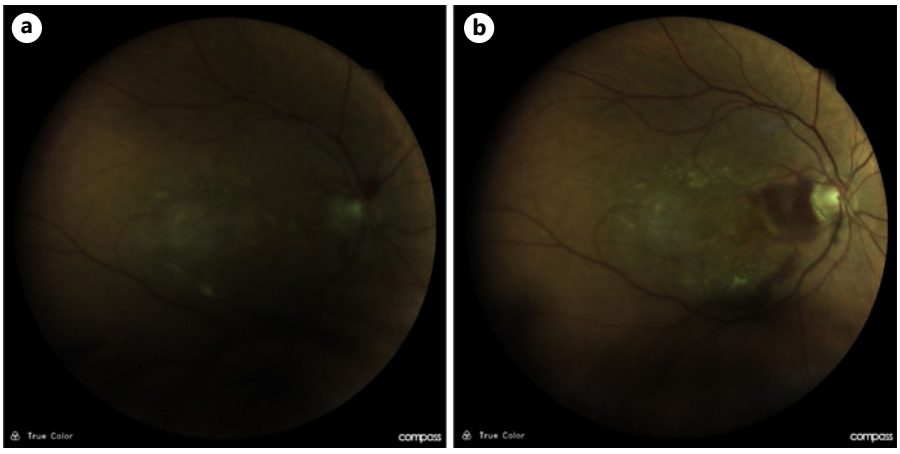

Fig. 4. a Case 4: an 81-year-old male patient. Color fundus photo of the right eye shows vitreous hemorrhage and macular changes at first presentation. **b** Color fundus photograph shows that the vitreous hemorrhage cleared after 1 dose of subtenon citrate PRP + bevacizumab injection and 10 sessions of MagnoVision. Peripapillary hemorrhage due to juxtapapillary choroidal neovascular membrane and macular scarring began to appear.

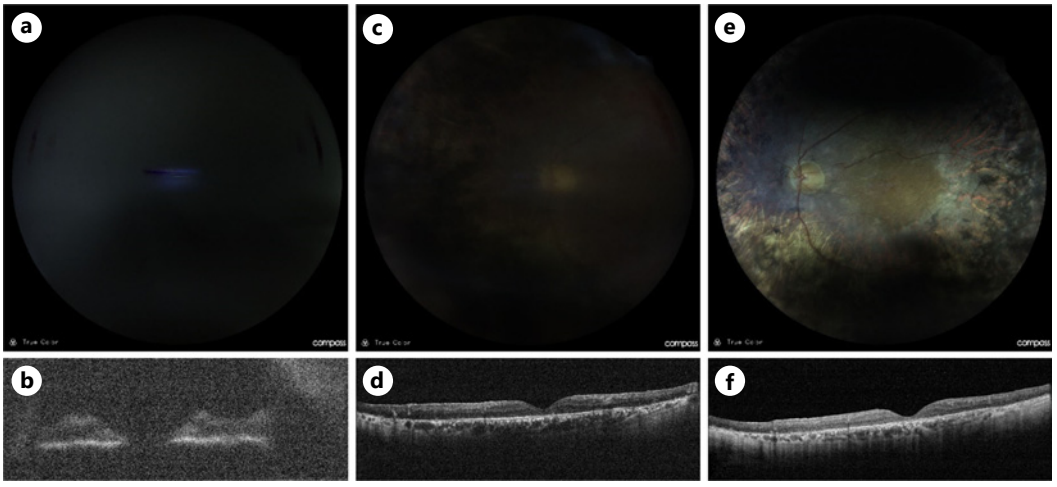

Fig. 5. a, **b** Case 5: a 52-year-old male patient. Color fundus photo and OCT of the left eye show dense vitreous hemorrhage at first presentation. **c**, **d** Color fundus photography and OCT show that vitreous hemorrhage began to decrease after 1 dose of subtenon citrate PRP + bevacizumab injection and 5 sessions of MagnoVision treatment. **e**, **f** Color fundus photography and OCT show that the vitreous hemorrhage has cleared up significantly after 10 sessions of MagnoVision treatment. Pigmentary changes of retinitis pigmentosa can be seen clearly in detail.

The patient's right eye received a subtenon injection of 1.0 mL of autologous citrated PRP solution + 0.5 mL of bevacizumab as treatment. MagnoVision was applied for 30 min immediately after the injection and once a day for 9 days. Bromelain tablets were started orally twice daily. By the 5th session, the vitreous hemorrhage had mostly cleared, and an extrafoveal polyp-like lesion was observed (Fig. 6b). After the 10th session, VA improved to 0.5 BCVA in the treated right eye, and the polypoid choroidal vasculopathy became flattened and scarred without any additional anti-VEGF injections (Fig. 6c).

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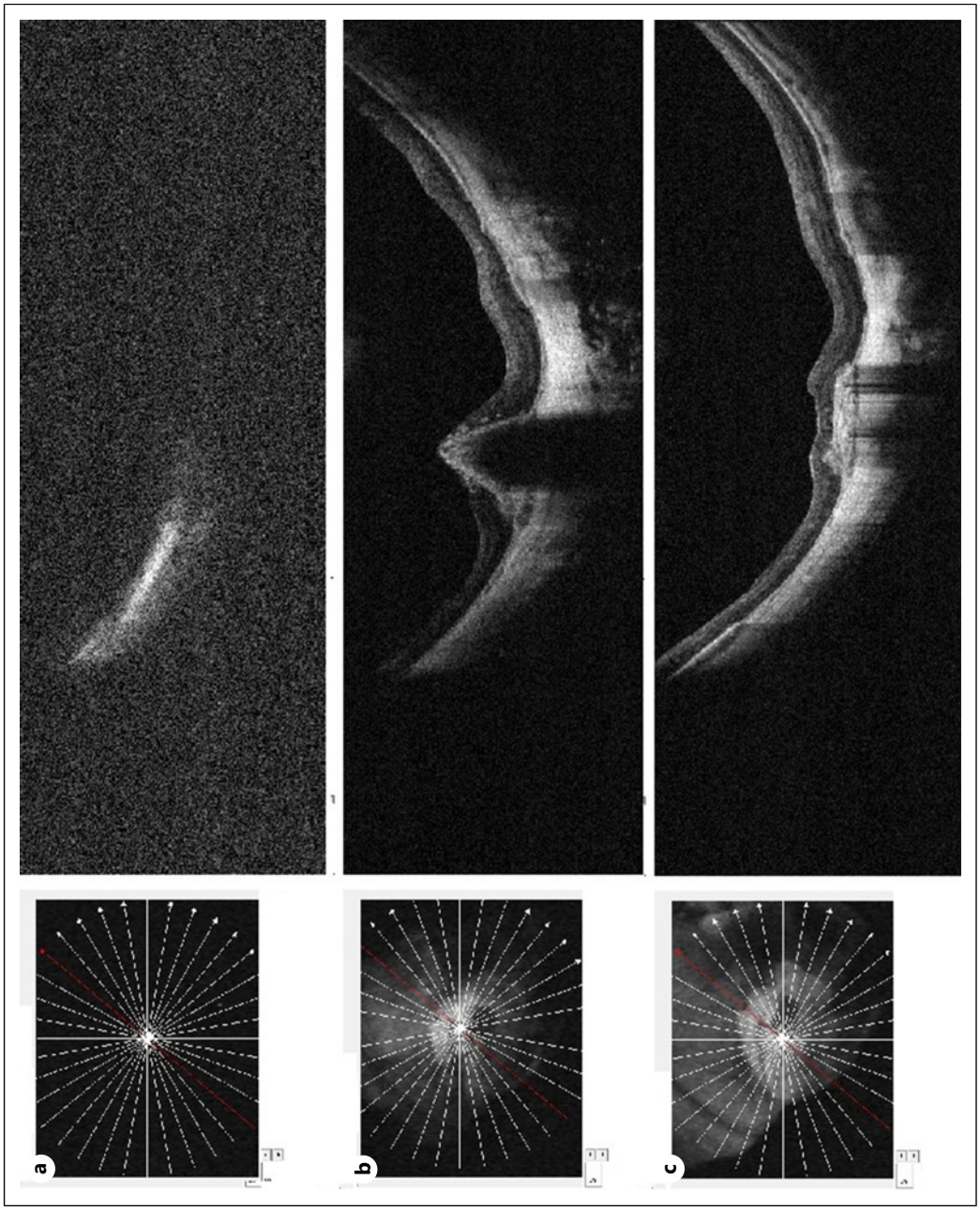

Fig. 6. a Case 6: a 71-year-old male patient. OCT of the right eye shows dense vitreous hemorrhage at first presentation. **b** OCT shows that vitreous hemorrhage began to decrease after 1 dose of subtenon citrate PRP + bevacizumab injection and 5 sessions of MagnoVision treatment. Extrafoveal polypoid choroidal neovascular membrane (CNV) became visible. **c** OCT shows that the vitreous hemorrhage cleared up significantly after 10 sessions of MagnoVision. Polypoidal CNV was flattened and scarred without additional anti-VEGF application.

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Discussion

Delayed resolution and clearance of retinal and vitreous hemorrhages may have several causes. The main cause is that the hemorrhage accumulates as a coagulum, and erythrocytes and cellular debris accumulate in a very cohesive clot. Additionally, there may be dysfunction of the RPE pump due to underlying pathologies. For example, in AMD, RPE cells have impaired phagocytosis, leading to drusen formation, and DR also causes RPE dysfunction as a result of capillary ischemia and neuroinflammation.

In addition, recurrence of the hemorrhage due to the underlying neovascular pathology might prolong the clearance of the hemorrhage. Furthermore, the hemorrhagic coagulum may become trapped within dense vitreous fibers or in the sub-ILM or subretinal compartments. Therefore, a combined treatment approach that covers all these causes might allow rapid clearance of vitreous and retinal hemorrhages, allowing earlier correct diagnosis and intervention [1–5].

Citrate is a well-known and reliable anticoagulant that breaks up the coagulum clot, allowing the erythrocytes and fibrin to become free [11]. It is found in a sterile form in PRP kits during the preparation of PRP [12]. PRP is a natural serum that accelerates wound healing after blood clotting and is used for various therapeutic purposes. It is a suspension containing 30 different growth factors and cytokines (primarily epithelial growth factor), which are released from platelets in the form of vesicles [7, 12]. Clinical and preclinical studies have shown that it accelerates the pump activity and phagocytosis function of the RPE [7, 8, 10, 13, 14].

PRP can be obtained autologously by taking blood from the patient or allogeneically by taking blood from a healthy blood donor with the same blood type. Diabetes mellitus, smokers, and the presence of autoimmune or infectious diseases necessitate the allogeneic use of PRP [12]. For preparing PRP, 4 mL of blood taken from the arm is transferred to a sterile citrate tube and centrifuged for 8 min at +4.0°C (at 2,500 rpm in a refrigerated centrifuge). Approximately 1 mL of plasma just above the erythrocytes and buffy coat in the tube is withdrawn into a 2.5-mL sterile syringe.

Bevacizumab is preferred as an anti-VEG because it can be obtained in sufficient volume and is well tolerated in subtenon injection. 0.5 mL of bevacizumab is drawn into 1 mL of PRP serum in the same syringe [15]. Anti-VEGF is used to prevent new hemorrhages and new leaks due to underlying vascular pathologies. After sufficient instillation of topical anesthesia drops that have been freshly opened and stored in the cold chain, 1.5 mL of PRP + anti-VEGF is injected into the supero-temporal subtenon space with the patient on a stretcher in an office environment.

Electromagnetic iontophoresis is the most important step in this new treatment approach. For this purpose, the MagnoVision™ device was used. The device has three basic functions. The first function is to increase the passage of the administered drugs from the subtenon space to the subretinal area via scleral pores and tyrosine kinase receptors. This is accomplished by vibrating the electrical charges of the drug molecules (iontophoresis). The second function is the liberation of erythrocytes by microvibration, their escape from compartments, and their movement towards the RPE (iontophoresis). Erythrocytes are very sensitive to electromagnetic iontophoresis because they contain iron atoms [16]. The third function of MagnoVision is to stimulate ion channels in neurons and create external action potentials. This feature contributes to the transition of neurons from OFF mode to ON mode in optic nerve diseases and to the reactivation of photoreceptors in the dormant phase of retinal degenerations. This feature is called neuromodulation. MagnoVision is contraindicated for patients with epilepsy and cardiac pacemakers [6–10]. The application and operating principles of the MagnoVision electromagnetic iontophoresis device are available in the online supplementary video.

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Tablets of bromelain (500 mg) were given orally to the patients twice a day (morning and evening) on an empty stomach for 1 month. Bromelain is a natural enzyme derived from pineapple fruit that has been shown to cause chemical vitreolysis [17, 18]. It may help release erythrocytes trapped between dense vitreous fibers and enhance the effect of electromagnetic iontophoresis.

In our case series, all cases achieved clinical visual improvement in the 10th session of electromagnetic iontophoresis while receiving subtenon anti-VEGF + citrated PRP + systemic bromelain. In all cases, the macular area was cleared in the 10th session, while in 2 cases, complete clearance of hemorrhage took 1 month.

Conclusion

Combined use of electromagnetic iontophoresis, subtenon PRP and bevacizumab injection, and oral bromelain can be considered an effective and safe new treatment method for vitreous and retinal hemorrhages without any need for surgical intervention. Beneficial effects of electromagnetic iontophoresis along with appropriate medications were demonstrated in 6 different patient groups with vitreous and retinal hemorrhages. With this novel, nonsurgical, effective, and reliable application, it is possible to clear most of the hemorrhages by around the 10th day, which allows us to make an early diagnosis and provide proper treatment of underlying pathologies. The method is quite safe, and we did not observe any adverse effects or complications in any patient. These positive and encouraging results warrant controlled group studies. If the hemorrhages are not sufficiently cleared after 10 sessions, the periods and injections can be extended to 3 periods, or doses can be repeated, and intervals can be changed according to personal experience.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material.

Statement of Ethics

Ethics Committee approval for the repetitive electromagnetic iontophoresis study was obtained from the Ankara University Faculty of Medicine Clinical Research Ethics Committee (12-971-21) and the Review Board of the Drug and Medical Device Department within the Turkish Ministry of Health (2021-618). Written informed consent was obtained from all of the patients for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Umut Arslan participated in the design of the study and performed procedures. Researcher Deniz Arslan reviewed medical records and wrote original draft of case reports. Dr. Emin Özmert revised and approved the final manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this published article and supporting images. Further inquiries can be directed to the corresponding author.

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