Pneumatic Displacement of Subretinal Hemorrhage Without Tissue Plasminogen Activator

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Objective: To assess the efficacy and complications of intravitreal injection of perfluoropropane gas for displacement of subretinal hemorrhage (SRH), without the use of tissue plasminogen activator.

Patients and Methods: Pure perfluoropropane gas (0.4-0.5 mL) was injected into the vitreous cavity in 5 patients with SRH involving the fovea because of age-related macular degeneration (4 eyes) or ruptured retinal arterial macroaneurysm (1 eye). The patients were instructed to maintain a prone position.

Results: Visual acuity ranged from 20/300 to 20/2000 before gas injection. On the day after gas injection, SRH was dramatically displaced in 3 eyes and slightly displaced with a reduction in the thickness of subfoveal hemorrhage in the remaining 2 eyes. Final visual acuity improved in all cases, ranging from 20/15 to 20/220. Three eyes had a final visual acuity of 20/50 or better. Vitreous hemorrhage caused by migration of SRH into the vitreous cavity and retinal detachment each occurred in 1 eye, and both complications were successfully treated by vitrectomy.

Conclusions: Gas injected into the vitreous cavity can displace SRH without the use of tissue plasminogen activator in some cases. Visual acuity after gas injection may be improved, making this treatment an alternative to evacuation of SRH with vitrectomy.


The natural course of subfoveal hemorrhage caused by age-related macular degeneration or macroaneurysms has been associated with a poor visual outcome.1-3 Vitreous surgery was first reported as a potential treatment for subfoveal hemorrhage in 1987, with mixed results,4 and despite continued improvements in surgical technique, such as the use of a small retinotomy, tissue-type plasminogen activator (tPA), and perfluorocarbon liquid, final visual outcomes have generally continued to be disappointing.5-10 Subretinal surgical interventions induce trauma on the sensory retina and retinal pigment epithelium, possibly contributing to poor outcomes. Improved surgical techniques that minimize subretinal manipulation seem to reduce the damage suffered by the sensory retina and retinal pigment epithelium.5 While clearance of subretinal hemorrhage (SRH) from the fovea is essential to improve foveal function, it has not been determined whether actual evacuation of SRH from the subretinal space is necessary. If clearance of SRH from the fovea could be achieved with an intervention less traumatic to the sensory retina and retinal pigment epithelium, foveal function would be expected to be restored.

Recently, Heriot11 reported that SRH was displaced by injecting tPA and long-acting gas into the vitreous cavity. We experienced 2 cases in which massive SRH moved to the anterior chamber after vitrectomy, lensectomy, peripheral retinotomy, and injection of perfluoropropane gas without the use of tPA followed by face-down positioning.12 In light of the report by Heriot, we hypothesized that SRH could be moved by gas injection into the vitreous cavity after face-down positioning without the use of tPA. This technique may be less traumatic to the retina and therefore may have advantages over vitrectomy. Herein we report the results of perfluoropropane injection into the vitreous cavity without use of tPA in the treatment of subfoveal hemorrhage.

REPORT OF CASES

CASE 1

A 64-year-old woman with age-related macular degeneration had undergone vitreous surgery 3 times for a subfoveal hemorrhage in her left eye in 1994 at another facility. In September 1996, she experienced a sudden decrease of vision in her right eye and visited her ophthalmologist.
One week after the onset of symptoms in the right eye, she was referred to our hospital. On our initial examination, corrected visual acuity was 20/40 OD and counting fingers in the left eye. Fundus examination of the right eye showed SRH around the disc sparing the fovea, and on the left there was silicone oil filling the vitreous cavity and a macular disciform scar. However, 4 days later, visual acuity decreased to 20/400 OD. The SRH had increased to a size of 48 disc areas and involved the central macula (Figure 1, A). Therefore, after obtaining informed consent, we performed intravitreal injection of 0.4 mL of pure perfluoropropane to her right eye, and she was instructed to maintain a prone position.

Twelve hours after gas injection, the SRH had shifted inferiorly, with an improvement of visual acuity to 20/100. Two days after injection, the SRH and sub-retinal pigment epithelial hemorrhage had moved further, and the subfoveal hemorrhage had become remarkably thinner, with an improvement of visual acuity to 20/70 (Figure 1, B). Vitreous opacity gradually increased, presumably because of migration of SRH into the vitreous cavity, and visual acuity had deteriorated to 20/2000 one week after gas injection. Because the vitreous opacity did not clear, vitrectomy was performed 19 days after gas injection. No retinal breaks were found, and the surgery was accomplished without creation of retinal breaks or use of any subretinal surgical procedures. Despite the formation of subretinal fibrosis between the disc and the macula, presumably because of residual SRH in this region, visual acuity had improved to 20/30 two months after gas injection and was 20/15 at the most recent visit, 13 months after gas injection (Figure 1, C).

**CASE 2**

A 63-year-old woman with retinal arteriolar macroaneurysm had a sudden decrease of vision in her left eye and was referred to our clinic. On initial examination, corrected visual acuity was 20/20 OD and 20/300 OS. Fundus examination disclosed a subfoveal hemorrhage with a...
total size of 11 disc areas, accompanied by preretinal hemorrhage of approximately 1 disc area (Figure 2, A). She underwent intravitreal injection of 0.4 mL of pure perfluoropropane gas 6 days after the onset of visual loss. On the day after gas injection, the SRH had shifted by approximately 3 disc diameters inferotemporally, and hemorrhage beneath the fovea was thinner (Figure 2, B), with an improvement of visual acuity to 20/200. The appearance of the preretinal hemorrhage had not changed. The SRH continued to move more peripherally (Figure 2, C), and visual acuity was 20/70 at 1 month and 20/40 at 2 months postoperatively (Figure 2, D). Sensitivity of the fovea measured by the Humphrey perimeter (Allergan-Humphrey Medical Instruments, Irvine, Calif) also improved from 13 dB before injection to 27 dB 2 months after gas injection.

**CASE 3**

A 56-year-old man with age-related macular degeneration noted a sudden decrease of vision in his left eye. Visual acuity was initially 20/70 OS but continued to deteriorate during the next 4 days. On examination after referral to our clinic in November 1996, corrected visual acuity was 20/20 OD and 20/2000 OS. Fundus examination disclosed an SRH of 21 disc areas in his left eye, with involvement of the fovea (Figure 3, A). Intravitreal injection of 0.5 mL of pure perfluoropropane gas was performed and face-down positioning was recommended. The SRH moved temporally the next day (Figure 3, B). Retinal detachment caused by a retinal tear in the inferotemporal quadrant occurred 4 days after gas injection.

**Figure 2.** A, Preoperative fundus photograph of a 63-year-old woman (patient 2) with retinal arteriolar macroaneurysm and subretinal hemorrhage. Visual acuity was 20/300. B, On the day after gas injection, the subretinal hemorrhage was displaced approximately 3 disc diameters inferotemporally, and subfoveal hemorrhage appeared thinner, while preretinal hemorrhage had not moved. Visual acuity had improved to 20/200. C, Three days after gas injection, subretinal hemorrhage had moved more anteriorly. D, Two months after gas injection, subretinal hemorrhage had disappeared from the macula, leaving punctate white deposits. Visual acuity had improved to 20/40.
jection. Vitrectomy and lensectomy were performed to reattach the retina, and SRH was removed intraoperatively from an intentional retinal break followed by intraocular tamponade with 20% sulfur hexafluoride. At last follow-up, 13 months after gas injection, the retina remained attached and visual acuity was 20/200 OS.

CASE 4

A 61-year-old woman with age-related macular degeneration had a sudden loss of vision in her left eye and was referred to our hospital 4 days later. Examination showed a corrected visual acuity of 20/400 OS, a subfoveal hemorrhage slightly less than 2 disc areas, and an associated hemorrhagic pigment epithelium detachment (Figure 4, A). Pure perfluoropropane (0.4 mL) was injected into the vitreous cavity with the patient under retrobulbar anesthesia. The next day, the SRH had moved slightly nasally and the thickness of subfoveal hemorrhage had decreased (Figure 4, B). Visual acuity had improved to 20/100, with further improvement to 20/30, eight days after gas injection. Visual acuity had deteriorated slightly to 20/50 at last follow-up, consistent with mild vitreous opacity that was present.

CASE 5

A 72-year-old man with age-related macular degeneration had a sudden loss of vision in his right eye. He came to our clinic 18 days later, with a corrected visual acuity of 20/700 OD. Fundus examination showed an SRH of 12 disc areas, with both red and yellowish-white portions, suggesting chronicity (Figure 5, A). Pure perfluoropropane gas was injected into the vitreous cavity. Although the position of the SRH did not markedly change, there was a slight inferior shift, and the thickness of the subfoveal portion decreased (Figure 5, B). Visual acuity improved to 20/220 in 1 week.

RESULTS

The results are summarized in the Table. Preoperatively, visual acuity ranged from 20/300 to 20/2000. In 3 of 5 eyes, subretinal hemorrhage was dramatically displaced from the fovea on examination the day after gas injection and continued to move more peripherally during the next several days (Figures 1 through 3). In the other 2 eyes, the SRH was partially displaced, with a clear reduction of the thickness of hemorrhage beneath the fovea (Figures 4 and 5). The height of the gas bubble in the vitreous cavity was between one third and one fourth of the vitreous cavity in all eyes.

On the day after gas injection, visual acuity had improved by 3 or more lines of Landolt C acuity chart in 2 of the 4 eyes in which it was measured. Best visual acuity achieved after gas injection was 20/40 or better in 3 of the 5 treated eyes. Final postoperative visual acuity improved by 3 or more lines in all 5 cases, ranging from 20/15 to 20/220, and was 20/50 or better in 3 eyes.
Complications after gas injection requiring surgery occurred in 2 eyes: vitreous hemorrhage caused by migration of SRH into the vitreous in 1 eye, and retinal detachment in 1 eye. Both complications were treated successfully.

In our series, SRH was dramatically displaced from the fovea shortly after injection of perfluoropropane gas without the use of tPA in 3 of 5 eyes. In addition to anatomical improvement at the fovea, visual function also dramatically improved postoperatively after gas injection in most cases. Most important, our visual results compare favorably with those in eyes treated with surgical evacuation of SRH. However, the small size of this study prevents adequate statistical comparisons.

Three of the 5 cases showed marked movement of SRH from the fovea. Small movement was seen in the other 2 cases, in which decreased thickness of subfoveal hemorrhage was associated with an improvement in visual acuity. We believe that gas injected into the vitreous cavity pushed or rolled SRH outward from the fovea. In patients able to maintain a strict face-down position, SRH would be expected to move anteriorly equally in all directions; in a position with the head tilted slightly forward, the SRH would be expected to move primarily in an inferior direction. Most patients maintained prone positioning for 2 weeks. However, strict prone positioning seems to be needed only for the first several days because the SRH was displaced within a short period in most cases.

The size of the hemorrhage may influence the efficacy of gas injection as a treatment for SRH. In case 4, despite gas injection just 4 days after the onset of symptoms, the hemorrhage was displaced the least of any of our cases. The size of the SRH in case 4 was less than 2 disc areas, which was much smaller than hemorrhages in our other cases. Because the gas bubble expands to cover a fundus area of greater than 90° when 0.4 mL of pure perfluoropropane is injected, a small SRH may not be effectively rolled or pushed by the gas bubble. We also found in our series that preretinal hemorrhage does not appear to be moved by the gas bubble (case 2), and this may also relate to small size. Takebayashi et al described a patient with age-related macular degeneration whose vision recovered by reduction of macular edema and displacement of preretinal hemorrhage after injection of sulfur hexafluoride into the vitreous cavity.

**Clinical Profile of the 5 Consecutive Patients With Subretinal Hemorrhage Who Received Gas Injection**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Diagnosis</th>
<th>Area of SRH, Disc Area</th>
<th>Symptoms to Gas Injection, d</th>
<th>Gas Injected</th>
<th>Visual Acuity</th>
<th>Final Postoperative</th>
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<tr>
<td>1/F/64 AMD</td>
<td>48</td>
<td>4</td>
<td>100% perfluoropropane, 0.4 mL</td>
<td>20/400</td>
<td>20/100</td>
<td>20/15</td>
</tr>
<tr>
<td>2/F/63 MA</td>
<td>11</td>
<td>6</td>
<td>100% perfluoropropane, 0.4 mL</td>
<td>20/300</td>
<td>20/200</td>
<td>20/40</td>
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<td>4/F/61 AMD</td>
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<td>20/400</td>
<td>20/100</td>
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<tr>
<td>5/M/72 AMD</td>
<td>12</td>
<td>18</td>
<td>100% perfluoropropane, 0.4 mL</td>
<td>20/700</td>
<td>20/500</td>
<td>20/220</td>
</tr>
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</table>

*SRH indicates subretinal hemorrhage; AMD, age-related macular degeneration; VH, vitreous hemorrhage; MA, retinal macroaneurysm; and RD, retinal detachment.*
The timing of gas injection may be critical for the success of this treatment. All eyes were treated within 6 days of the onset of symptoms, except for case 5, in which the patient was treated 18 days after suffering a loss of vision. Despite being of appropriate size, the SRH in that eye was only minimally displaced by gas injection. Patients with SRH who are examined long after the onset of symptoms may not be good candidates for gas injection and should perhaps be considered for surgical intervention.17,18

Most of the recent reports describing the surgical evacuation of SRH involve the use of tPA.3-7,15 The fibrinolytic action of tPA makes it effective in the lysis of subretinal clots, allowing the use of a small retinotomy, presumably reducing retinal damage during vitrectomy. Visual results of vitrectomy for SRH with the use of tPA seem to be better than previous techniques, but no controlled studies have been performed with tPA, and its benefit for visual outcome has not been definitively established.6 Injection of tPA into the vitreous cavity was used without vitrectomy to treat SRH in an animal model.16 Subsequently, Heriot11 reported a technique for the treatment of SRH in which tPA and a long-acting gas were injected into the vitreous cavity, with the goal of clot lysis and displacement of the liquefied hemorrhage. However, tPA may not be essential in our technique. If gas is injected into an eye with a relatively fresh hemorrhage, the clot may be soft enough to allow sufficient movement for recovery of foveal function. This may not be true in cases with more solid clots, such as our case 5, which demonstrated the least visual improvement of eyes in our series, and in which tPA could have potentially facilitated clot displacement. On the other hand, tPA is not free of untoward effects; it may induce rebleeding when it is injected within 3 days of the original hemorrhage,17 and retinal toxic effects from tPA have been reported.18,19 Therefore, injection of gas and tPA may be indicated for patients with older SRH, but tPA may not be necessary in patients with relatively newer SRH.

Our visual results in this small series were promising. Preoperative visual acuity ranged from 20/300 to 20/2000. Final postoperative visual acuity had improved by 3 or more lines in all eyes, and 3 patients achieved an acuity of 20/50 or better. In submacular surgery, surgical manipulations, including creation of a retinotomy, injections into the subretinal space, and aspiration of subretinal fluid and hemorrhage, induce trauma to the retina and retinal pigment epithelium. In our technique, direct surgical trauma to macular tissues is avoided. Additionally, the movement of SRH is presumably much slower than that in subretinal surgery with vitrectomy. The very slow movement of SRH may reduce retinal damage, resulting in better visual outcome. These 2 factors may have accounted for the more normal postoperative appearance of the macula seen after gas injection alone than in many of our own or reported cases of eyes undergoing subretinal surgery.

Vitreous hemorrhage that required vitrectomy occurred in 1 eye. Migration of SRH into the vitreous cavity has been documented in clinical reports and animal experiments.16,20 Larger hemorrhages have a higher incidence of migration into the vitreous cavity.16 Gas injection may promote migration of SRH into vitreous cavity. However, vitreous hemorrhage can usually be removed safely by simple vitrectomy, with a low risk of further complications and the avoidance of any subretinal manipulation that may damage the sensory retina.

A retinal break occurred in 1 eye and resulted in a retinal detachment with proliferative vitreoretinopathy, which was successfully treated by vitreous surgery. Retinal tear formation is a well-known complication of intravitreal gas injection, occurring in 7% to 23% of eyes after pneumatic retinophy.21-24 If retinal breaks or degeneration are found in the inferior quadrant, gas injection should not be performed because most new breaks are found inferiorly. Postoperative retinal detachment, usually associated with proliferative vitreoretinopathy, has also been reported after vitrectomy for SRH.5,6,8,10 The risk of proliferative vitreoretinopathy may be greater than when vitrectomy is done for other diseases, because performance of a retinotomy may release growth factors that can stimulate chemotaxis of retinal pigment epithelial cells.25

We have shown that SRH can be displaced by gas injection without the use of tPA in some cases. In our small case series, patients seem to obtain better visual function after gas injection than after vitrectomy and mechanical removal of hemorrhage. Because our technique is simple and can achieve good results, we believe it may be a good first treatment in appropriate cases of SRH. Efficacy may be limited in eyes with small SRH or delayed diagnosis of SRH. Vitrectomy with the use of tPA should be considered in cases in which SRH is not displaced within 2 to 3 days of gas injection. Additional study is needed to further define indications of this new treatment.

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<tr>
<th>Follow-up, mo</th>
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<tr>
<td>14</td>
<td>VH</td>
<td>Vitrectomy</td>
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<td>No</td>
</tr>
<tr>
<td>13</td>
<td>RD</td>
<td>Vitrectomy</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
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A substantial proportion of cases of glaucoma have a genetic basis. Mutations causing glaucoma have been identified in the chromosome 1 open-angle glaucoma gene (GLC1A). The spectrum of disease can range from juvenile glaucoma to typical late-onset primary open-angle glaucoma.

**Clinical Features Associated With Mutations in the Chromosome 1 Open-Angle Glaucoma Gene (GLC1A)**

**Background:** A substantial proportion of cases of glaucoma have a genetic basis. Mutations causing glaucoma have been identified in the chromosome 1 open-angle glaucoma gene (GLC1A), which encodes a 57-kd protein known as myocilin. The normal role of this protein and the mechanism by which mutations cause glaucoma are not known.

**Methods:** We screened 716 patients with primary open-angle glaucoma and 596 control subjects for sequence changes in the GLC1A gene.

**Results:** We identified 16 sequence variations that met the criteria for a probable disease-causing mutation because they altered the predicted amino acid sequence and they were found in one or more patients with glaucoma and in less than 1 percent of the control subjects. These 16 mutations were found in 33 patients (4.6 percent). Six of the mutations were found in more than 1 subject (total, 99). Clinical features associated with these six mutations included an age at diagnosis ranging from 8 to 77 years and maximal recorded intraocular pressures ranging from 12 to 77 mm Hg.

**Conclusions:** A variety of mutations in the GLC1A gene are associated with glaucoma. The spectrum of disease can range from juvenile glaucoma to typical late-onset primary open-angle glaucoma.

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