

Clinical science

The birth weight and PMA of the neonates with zone I and posterior zone II disease in our series is higher than reports from similar series from developed countries. Carden *et al*²² reported that 58 infants referred to the National Hospital of Paediatrics in Hanoi, Vietnam with ROP had birth weights ranging from 800–1900 g and gestational ages ranging from 28–35 weeks. Gu *et al*²³ reported birth weights of infants with ROP in China ranging from 1501–2000 g. Risk factors reported to cause ROP in more mature neonates are septicaemia and poorly controlled oxygen therapy.

Our study showed that 55% of eyes continued to have incomplete vascularisation at time of follow-up examination including up to 259 weeks after birth. In the eyes with the longest IVB-FA interval (case no. 10) there were also numerous areas of lattice degeneration, which may increase the future risk for development of retinal tears and complications after cataract surgery, as has been previously reported.^{24 25} Although we did not see ridges or extraretinal fibrovascular proliferation in these 11 eyes, there was fluorescein leakage at the vascular-avascular border in 9 eyes. This may be important, as fluorescein leakage has previously been reported to be a sign of progression to severe ROP.¹⁹

In conclusion, our study demonstrates that although intravitreal bevacizumab can be very effective in causing resolution of zone I and posterior zone II ROP, ophthalmologists should remain cautious as infants may remain at risk due to avascular peripheral retinas even many years after treatment. Careful examination using FA allows accurate visualisation of risk factors such as the extent of avascular retina and the presence of dye leakage.

Contributors All work carried out for this study was performed by the listed authors. Review of medical records and fluorescein angiogram digital recordings by SGT and RH. Clinical science and editorial input by GCL (pediatric ophthalmologist) and SK. PGM went over the manuscript numerous times to provide editorial input.

Competing interests None.

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Fluorescein angiographic observations of peripheral retinal vessel growth in infants after intravitreal injection of bevacizumab as sole therapy for zone I and posterior zone II retinopathy of prematurity

Sjakon G Tahija, Rini Hersetyati, Geoffrey C Lam, et al.

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Efficacy of Short-term Postoperative Perfluoro-n-octane Tamponade for Pediatric Complex Retinal Detachment

AYAKO IMAIZUMI, SHUNJI KUSAKA, HIROE NOGUCHI, YOSHIKAZU SHIMOMURA, AND SHOICHI SAWAGUCHI

- **PURPOSE:** To evaluate the efficacy of perfluoro-n-octane as a postoperative short-term tamponade after vitrectomy in pediatric cases with complex retinal detachment (RD) and proliferative vitreoretinopathy (PVR).
- **DESIGN:** Prospective, noncomparative, interventional case series.
- **METHODS:** The medical records of 10 eyes of 9 children (6 boys and 3 girls), whose age ranged from 3 months to 11 years, with a median of 7.5 months, were reviewed. The cause of the PVR was retinopathy of prematurity (7 eyes of 6 patients); familial exudative vitreoretinopathy; or tractional RD associated with congenital optic nerve anomalies,¹ and persistent fetal vasculature. Perfluoro-n-octane was injected into the eyes at the primary surgery in 2 eyes and at the repeat surgeries in 8 eyes. The perfluoro-n-octane was removed after 1 to 4 postoperative weeks. The patients were followed for 5 to 43 months.
- **RESULTS:** At the last examination, the retinas were reattached in 8 eyes (80%). In the other two eyes, a retinal attachment was not obtained. Postoperatively, the best-corrected visual acuity improved from hand motion to 0.1 in 1 eye and could not be measured in the other 9 patients because of their ages. No apparent adverse events related to the use of perfluoro-n-octane were noted.
- **CONCLUSIONS:** Although cautions should be exercised regarding potential mechanical retinal injuries by heavy liquids in the eye, short-term perfluoro-n-octane tamponade was effective in pediatric cases with severe PVR in which retinal reattachment is considered to be difficult with conventional gas or silicone oil tamponade. (Am J Ophthalmol 2014;157:384–389. © 2014 by Elsevier Inc. All rights reserved.)

PEDIATRIC RETINAL DETACHMENTS (RDS) HAVE many characteristics that are distinct from adult RDs. One of these characteristics is that they are more often associated with congenital or developmental

abnormalities, such as familial exudative vitreoretinopathy (FEVR), tractional RD associated with congenital optic nerve anomalies, persistent fetal vasculature, or retinopathy of prematurity (ROP), than are adult RDs. One other characteristic is late detection, which often means that the RDs are longstanding, have macular involvement and are associated with proliferative vitreoretinopathy (PVR).¹ These features make pediatric RDs complex and difficult to treat satisfactorily.

Long-acting gas and silicone oils are commonly used for postoperative tamponade to treat the severe rhegmatogenous retinal detachments (RRDs) associated with PVR. However, their effectiveness is limited when proliferative changes exist in the inferior retina because of their low specific gravity. Because of this, patients are requested to maintain a prone position for several days to weeks postoperatively. However, it is difficult to have an infant maintain this position for any length of time. For these cases, perfluoro-n-octane (C₈F₁₈), which has a specific gravity of 1.75, greater than that of water, theoretically should be more effective as a tamponade.

We report the surgical results of pediatric complex RRDs with PVR that underwent vitrectomy using perfluoro-n-octane as a short-term postoperative tamponade.

METHODS

THE MULTICENTER STUDY WAS PERFORMED IN ACCORDANCE with the tenets of the Declaration of Helsinki. The Institutional Review Board of the Naha City Hospital and Sakai Hospital Kinki University Faculty of Medicine approved this prospective study before the beginning of the study, and a written informed consent was obtained from the parents of all patients. The protocol of this study was in compliance with Health Insurance Portability and Accountability Act requirements.

A perfluoro-n-octane tamponade was used in 10 eyes of 9 young patients to treat various vitreoretinal disorders at the Naha City Hospital and the Sakai Hospital Kinki University Faculty of Medicine between August 2009 and January 2013. Of those patients, 1 eye of 1 patient had FEVR, 1 eye of 1 patient had an RD associated with congenital optic nerve anomalies,² 1 eye of 1 patient had persistent fetal vasculature, 6 eyes of 5 patients had stage 5 retinopathy of prematurity (ROP), and 1 eye of 1 patient had stage

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From the Department of Ophthalmology, Naha City Hospital, Okinawa, Japan (A.I., H.N.); the Department of Ophthalmology, Sakai Hospital Kinki University Faculty of Medicine, Osaka, Japan (S.K., Y.S.); and the Department of Ophthalmology, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan (A.I., S.S.).

Inquiries to Shunji Kusaka, Department of Ophthalmology, Sakai Hospital Kinki University Faculty of Medicine, 2-7-1 Harayamadai, Minami-Ku, Sakai, 590-0132 Osaka, Japan; e-mail: kusaka-ns@umin.net

TABLE. Characteristics of Patients and Results with Short-term Postoperative Perfluoro-n-octane Tamponade for Pediatric Proliferative Vitreoretinopathy

No.	Sex	Age	Disease	Number of vitrectomy before PFO tamponade	Period of PFO tamponade (weeks)	Anatomic results
1	Boy	11 Y	FEVR, PVR	5	3	RA
2	Girl	8 M	Stage 5 ROP	1	2	RA
		8 M	Stage 5 ROP	1	2	RA
3	Boy	3 M	Stage 5 ROP	1	2	RA
4	Boy	3 M	Stage 5 ROP	1	2	RA
5	Boy	1 Y	TRD associated with congenital optic nerve anomalies ¹	0	1	No RA (redetachment after 2 months of RA)
6	Boy	6 M	Stage 5 ROP	2	1	RA
7	Boy	16 M	PFV, PVR	1	3	RA
8	Girl	4 M	Stage 4 B ROP	0	4	RA
9	Girl	4 M	Stage 5 ROP	1	1	No RA

FEVR = familial exudative vitreoretinopathy; M = months-of-age; PFO = perfluoro-n-octane; PFV = persistent fetal vasculature; PVR = proliferative vitreoretinopathy; RA = retinal attachment; ROP = retinopathy of prematurity; TRD = tractional retinal detachment; Y = years-of-age.

4B ROP. The ages of the patients ranged from 3 months to 11 years, with a median of 7.5 months (Table). Of the patients, 3 were female children and 6 were male children.

Perfluoro-n-octane was used in 2 eyes at the primary operation; 1 with RD associated with congenital optic nerve anomalies and 1 with stage 4B ROP. Perfluoro-n-octane was used in the 8 other eyes at the time of the reoperation. The follow-up-period ranged from 5 to 43 months, with a median of 19.5 months.

All surgeries were performed by one surgeon (S.K.). A standard 3-port pars plana vitrectomy using 23-gauge instruments was performed. Pars plana lensectomy, membrane segmentation, delamination, and peeling were performed, depending on the condition of the retina. If the retinal detachment had a closed funnel shape in the ROP cases, a vitreous scissors and/or forceps were used to cut the anterior vitreous fibers and proliferative membranes to gain access to the midvitreous cavity and the optic disc. An encircling #240 silicone band was placed at the equator in 3 eyes: 1 eye with FEVR, 1 eye with RD associated with congenital optic nerve anomalies, and 1 eye with persistent fetal vasculature. The crystalline lens was removed in all of the cases.

During the reoperations, fibrous membranes were removed as completely as possible to relieve the traction on the retina. Then, perfluoro-n-octane was injected slowly through a 25- or 27-gauge blunt needle to fill the vitreous cavity with a single bubble. This was followed by laser ablation around the retinal breaks. The perfluoro-n-octane was left in the eye, and the sclerotomy sites were securely sutured.

The parents of the patients were instructed to try to keep their children in a supine or sitting position as much as possible for 1 to 4 weeks. Postoperatively, fundus examinations, slit-lamp examinations, and intraocular pressure measurements using iCare (Tiolat, Helsinki, Finland) or Tono-Pen XL (Reichert, Depew, NY, USA) were performed periodically. Then vitrectomy, with an exchange

of the perfluoro-n-octane by balanced salt solution (BSS plus) was performed with care being taken to ensure that all of the perfluoro-n-octane was removed. To remove as much of the perfluoro-n-octane as possible, we first aspirated the perfluoro-n-octane with BSS plus irrigation and then with air irrigation. A small amount of BSS plus was then injected onto the posterior retina. This then made the residual perfluoro-n-octane visible and easy to remove. If proliferative membranes were found, they were removed, and 10% to 20% sulfur hexafluoride (SF₆) or 10% perfluoropropane (C₃F₈) was used, according to the surgeon's decision.

In all patients, the perfluoro-n-octane tamponade duration was 1 to 2 weeks; however, it was delayed for 1 to 2 additional weeks in 3 eyes of 3 children because of their general medical conditions. One of these cases was an 11-year-old boy. The anatomic status of the retina, visual outcomes, and complications were assessed at the final follow-up examination.

RESULTS

• **CASE REPORT 1:** Case 1 was an 8-year-old boy who was referred to us for the treatment of a rhegmatogenous RD involving the macula of the right eye. Fundus examinations revealed a retinal break in the inferior temporal retina of the right eye and a peripheral avascular area with fibrovascular membranes in the temporal retina in both eyes. These findings suggested that the patient had FEVR in both eyes. The decimal best-corrected visual acuity (BCVA) was 0.04 in the right eye. The retina was reattached by scleral buckling; 6 months later, the BCVA had improved to 0.1 in the right eye.

Three years later, he developed a total retinal detachment with PVR in the right eye. A large tear of approximately

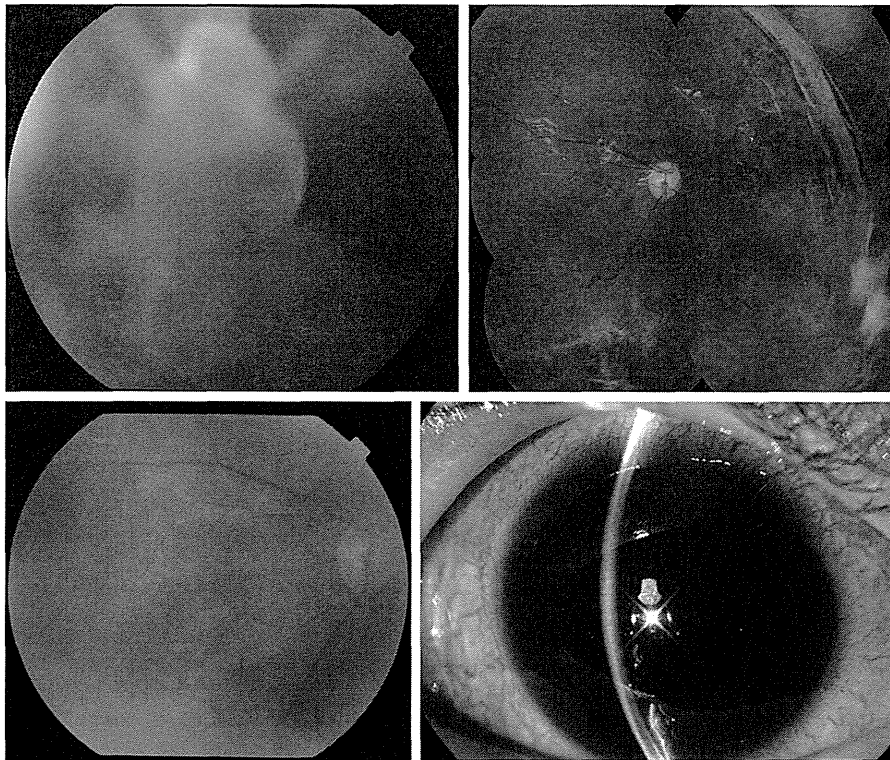


FIGURE 1. Case 1. Fundus photograph of the right eye of a patient with familial exudative vitreoretinopathy (FEVR). (Top left) fundus photograph of the right eye before the first vitrectomy, showing a total retinal detachment with PVR. (Top right) fundus photograph of the right eye before the sixth operation, showing a redetachment in the inferior retina due to re-proliferations. (Bottom left) 3 months after the last vitrectomy. BCVA was 0.01 in the right eye. (Bottom right) slit-lamp photograph 2 weeks after PFO tamponade, showing PFO bubbles in the anterior chamber.

60 degrees was present in the upper nasal peripheral retina. The BCVA was hand motion in the right eye. Because of the repeated detachments, vitrectomy with silicone oil or C_3F_8 gas tamponade was performed 5 times. Because all of the redetachments were due to proliferation in the inferior retina, we decided to use perfluoro-n-octane as a postoperative tamponade. During the sixth vitrectomy, perfluoro-n-octane was injected into the eye. The patient was instructed to rest in a supine or sitting position after the perfluoro-n-octane tamponade. After 2 weeks, multiple perfluoro-n-octane bubbles were noted in the inferior anterior chamber. The perfluoro-n-octane was removed 3 weeks later and replaced with 10% C_3F_8 gas tamponade. The retina remained reattached during the 43-month follow-up. The BCVA at the last visit was 0.1 in the right eye (Fig. 1).

• **CASE REPORT 2:** Case 2 was a premature female infant with a birth weight of 758 grams and a gestational age of 23 weeks. She was referred to us with a diagnosis of bilateral severe ROP at a postconception age of 41-weeks. She had undergone photocoagulation to the avascular retina in both eyes at the postconception age of 31 weeks. Despite confluent photocoagulation in the avascular area, the ROP continued to progress, and she was referred to the Naha City Hospital.

At the initial examination, the patient was found to have stage 5 ROP in both eyes. At the postconception age of 45 weeks, vitrectomy and lensectomy was performed in both eyes. During the vitrectomy, fibrous membranes were removed as completely as possible, but an iatrogenic retinal break occurred in each eye. This was followed by C_3F_8 gas tamponade in both eyes. The retinas of both eyes were found to be detached when the C_3F_8 gas disappeared. At the age of 8 months, a second surgery, involving membrane peeling and retinotomy, was performed on both eyes, followed by injection of perfluoro-n-octane, which was retained in both eyes. After 2 weeks, the perfluoro-n-octane was removed and replaced with a 20% SF_6 gas tamponade. The retinas of the both eyes remained attached during the 22 months of follow-up, although the visual acuity at the last visit was limited to light perception (Fig. 2).

For all eyes, the total number of operations, including those that occurred when the perfluoro-n-octane was removed, ranged from 2 to 7, with a median of 3. The perfluoro-n-octane was retained in the eye after the first surgery in 2 eyes, after the second surgery in 6 eyes, after the third surgery in 1 eye, and after the sixth surgery in 1 eye for 1 to 4 weeks (median, 2.0 weeks). The postoperative perfluoro-n-octane tamponade was used at the primary vitrectomy in 2 eyes of 2 patients; 1 eye with a tractional RD

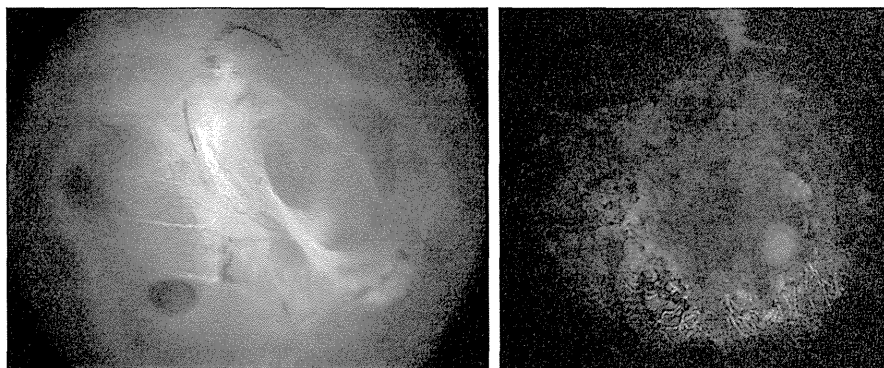


FIGURE 2. Case 2. Fundus photograph of the right eye of a patient with proliferative vitreoretinopathy (PVR). (Left) fundus photograph of the right eye after the first vitrectomy, showing total retinal detachment with PVR. (Right) fundus photograph of the right eye after PFO removal, showing reattachment of the retina.

associated with congenital optic nerve anomalies, and 1 eye with stage 4B ROP.

Because of the severe proliferation in the inferior retina, we believed it would be difficult to maintain the reattached retina by gas or silicone oil tamponade. In the other 8 eyes of 7 patients, perfluoro-n-octane tamponade was used at the time of reoperation after failure of retinal reattachment following a preceding vitrectomy using gas or silicone oil tamponade. Globule dispersion was noted in all of the eyes at the time of perfluoro-n-octane removal. During the perfluoro-n-octane tamponade, no eyes had intraocular pressures higher than 20 mm Hg or apparent intraocular inflammation.

At the latest examination, the retinas remained reattached in 8 of 10 eyes (80.0%). In 1 eye with tractional RD associated with congenital optic nerve anomalies (case 5), the perfluoro-n-octane was removed 1 week later, and the retina remained reattached for 1 month. However, 2 months after the perfluoro-n-octane was removed, a redetachment developed with severe PVR that was considered to be inoperable. In an eye with stage 5 ROP (case 9), a dense vitreous hemorrhage occurred after the primary vitrectomy. After 3 weeks, a reoperation was performed. At the second operation, extensive membrane removal was performed, followed by perfluoro-n-octane tamponade. After the second vitrectomy, vitreous hemorrhage occurred again despite the presence of perfluoro-n-octane in the eye. A third vitrectomy was performed 1 week later, and extensive membrane peeling was performed followed by C_3F_8 gas tamponade. However, 1 month later, the retina was totally detached, with severe PVR, which we considered inoperable.

DISCUSSION

POSTOPERATIVE PERFLUORO-N-OCTANE TAMPONADE WAS used for a short period in 10 eyes with pediatric complex RD, in which gas or silicone oil had been considered to

be ineffective because the posterior proliferative changes were in the inferior retina. Perfluoro-n-octane tamponade was used because we believed that it would be difficult for children to maintain a prone position for any length of time. The perfluoro-n-octane was left in all of the eyes for 1 to 4 weeks, and the retinas remained reattached after removal of the perfluoro-n-octane in 8 of the 10 (80%) eyes. Given the complexity of the RD in the patients, we consider these results to be relatively good.

Silicone oil has been widely used as a postoperative tamponade in pediatric patients. Despite the proven long-term safety profile of silicone oil, it has been reported to release mitogenic factors, and thus may be a causative factor in PVR.³ This would then lead to postoperative perisilicone proliferation, which can cause redetachment. In addition, the lower specific gravity of gas and silicone oil as compared to water makes their tamponade effect unsatisfactory for detachments of the inferior retina, especially in pediatric patients whose compliance with maintaining the prone positioning is poor.

In contrast, perfluoro-n-octane has a high specific gravity of 1.75, which should have a better tamponade effect in inferior or posterior retinal detachments than gas or silicone oil. An earlier study showed that perfluoro-n-octane is biologically inert and does not contain protonated impurities measurable by nuclear magnetic resonance spectroscopy.⁴ Also, perfluoro-n-octane appears to release fewer mitogenic factors than silicone oil.³ It has been proposed that mediators of cellular proliferation, pigmented cells, chemoattractants, and serum components could diffuse into the vitreous chamber and become concentrated in the small amount of aqueous fluid that is still present.⁵ Theoretically, heavy liquids should lift these mediators off the retinal surface, thereby preventing the development of PVRs.⁵

Another benefit of perfluoro-n-octane as a postoperative tamponade is the ease of its removal due to its lower viscosity of 0.58 mm²/s compared to silicone oil, which has a viscosity of 1000 to 5000 mm²/s.

Thus far, postoperative perfluoro-n-octane short-term tamponade has been used mainly for retinal detachments caused by giant tears.⁵⁻⁷ Sirimaharaj and associates⁶ reported that perfluoro-n-octane was effective for short-term postoperative tamponade to manage retinal detachments resulting from giant retinal tears. They elected to leave the perfluoro-n-octane in situ for 5 to 14 days because doing so provided sufficient time for chorioretinal adhesions to develop.⁶ Rofail and associates⁷ postulated that postoperative tamponade with perfluoro-n-octane decreases the rate of redetachments in eyes with giant retinal tears more than silicone oil or perfluorocarbon gas alone. To the best of our knowledge, there has been only 1 report on the use of perfluoro-n-octane for postoperative tamponade in eyes with a pediatric retinal detachment. Sick and associates⁸ used this technique in an infant with X-linked retinoschisis and complex retinal detachment. The retina was successfully reattached after removal of perfluoro-n-octane, which had been retained in the eye for 25 days without significant inflammation. It has been suggested that the lower rate of redetachments when using perfluorocarbon liquids as postoperative tamponade is due to the extended apposition of the retinal tear to the underlying retinal pigment epithelium, resulting in more effective chorioretinal adhesion by retinopexy.^{5,9} The incidence of inferior PVR was also lower after postoperative perfluorocarbon liquids tamponade, probably because of a lack of pooling of the retinal pigment epithelium cells, chemoattractants, and serum components over the inferior retina.^{5,10}

Sirimaharaj and associates⁶ reported that there were no serious adverse effects of perfluoro-n-octane as a postoperative tamponade. They also reported that the rate of cataract progression in their patients was 80.5%, which was comparable to the values in earlier reports of cataract progression (70% to 80%) after simple vitrectomy for an idiopathic epiretinal membrane.¹¹ Rofail and colleagues⁷

reported that the rate of postoperative complications after perfluoro-n-octane postoperative tamponade was equivalent to that after intraoperative perfluoro-n-octane.^{12,13} Thus, perfluoro-n-octane appears to be effective and safe as a postoperative tamponade as long as it is used for only a short period.

Animal studies have been conducted to determine the toxicity of perfluoro-n-octane as a tamponade substance. Chang and associates¹⁴ reported that perfluoro-n-octane left for 1 week in rabbit eyes induced mild histologic changes, including thinning of the outer plexiform layer. After 2 weeks, focal areas of narrowing of the outer plexiform layer and ultrastructural distortions of the photoreceptor outer segments in the inferior retina were noted. These changes became more pronounced after 1 and 2 months. Because similar changes have been reported in the superior retina in silicone-filled eyes, these changes may represent mechanical rather than toxic effects.¹⁴ Rabbit eyes injected with perfluoro-n-octane for 1 and 2 months had minimal lens changes, and they consisted of posterior subcapsular opacities in the portions of the lens capsule in contact with the perfluoro-n-octane liquid.⁶ On the other hand, rabbit eyes in which the perfluoro-n-octane was left in the vitreous cavity for longer than 1 week had varying degrees of globule dispersion.¹⁴ Similar findings were noted in all of the eyes in this study at the time of perfluoro-n-octane removal.

Taken together, the appropriate duration for postoperative perfluoro-n-octane tamponade seems to be approximately 1 to 2 weeks.

Although special caution should be exercised concerning the mechanical tamponade effects on the retina, it appears that short-term postoperative tamponade with perfluoro-n-octane is effective in pediatric cases with complex RD in which proliferations exist in the inferior or posterior retina.

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Biosketch

Ayako Imaizumi, MD, completed her residency in Ophthalmology at Osaka University Hospital. Currently she is the director of ophthalmology at Naha City Hospital and a postgraduate student at Graduate School of Medicine, University of the Ryukyus. Her field of interest includes surgical treatment of vitreoretinal disease such as diabetic retinopathy, retinal detachment, and retinopathy of prematurity.



Biosketch

Shunji Kusaka, MD is a Professor of Ophthalmology at Sakai Hospital Kinki University Faculty of Medicine, Sakai, Japan. Dr Kusaka completed his residency in Ophthalmology at Osaka University and his fellowship training in vitreoretinal surgery at Osaka National Hospital. After finishing research fellowship program at University of Michigan, he continues clinical research in vitreoretinal diseases in Japan. His research interests include treatment of various vitreoretinal disorders, especially pediatric retinal diseases.