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CLINICAL INVESTIGATION

Buckling surgery and supplemental intravitreal bevacizumab or photocoagulation on stage 4 retinopathy of prematurity eyes

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Abstract
Purpose To report the results of scleral buckling (SB) with or without photocoagulation (PC) and intravitreal bevacizumab (IVB) for stage 4 retinopathy of prematurity (ROP) eyes.
Methods Forty-two eyes of 28 patients with SB and/or PC or IVB were studied. Twenty-nine eyes had stage 4A and 13 eyes had stage 4B ROP. Seventeen eyes underwent SB combined with additional intraoperative or postoperative treatments (combined group). Twenty-five eyes underwent SB without additional therapy (non-combined group). The concentrations of vascular endothelial growth factor (VEGF) in the aqueous humor determined by enzyme-linked immunosorbent assay were compared between the two groups. The initial and final reattachment rates were also compared.
Results The gestational age and birth weight were 25.0 ± 2.0 weeks and 786 ± 222 g in the combined group, and 25.5 ± 2.1 weeks and 899 ± 315 g in the non-combined group. The postmenstrual age at the time of initial surgery was 38.0 ± 1.9 in the combined and 44.1 ± 4.0 weeks in the non-combined group ($P < 0.001$). The initial reattachment rate was 92 % in stage 4A and 75 % in stage 4B of ROP eyes in the combined group, and the rate was 93 % in stage 4A and 33 % in stage 4B of ROP eyes in the non-combined group. The mean VEGF concentration in aqueous humor was 1923 ± 779 pg/ml in the combined group and 985 ± 303 pg/ml in the non-combined group ($P < 0.05$).
Conclusion Our results show that the retinal reattachment rate after combined therapy was comparable to that in the non-combined group. We conclude that combined therapy may be effective even in ROP eyes with high activity.

Keywords VEGF · Bevacizumab · Retinopathy of prematurity · Scleral buckling · Photocoagulation

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Introduction

Early treatment by photocoagulation (PC) in eyes with retinopathy of prematurity (ROP) at stage 2 + or stage 3 of the International Classification has become standard therapy in recent years [1]. Scleral buckling (SB) surgery has been the conventional treatment of eyes with severe ROP at stage 4A or 4B even after PC has been performed. However, some eyes treated even at this earlier stage can still progress and develop proliferative membranes. It has recently been reported that pars plicata vitrectomy (PPV) with lens-sparing vitrectomy can lead to reattachment in eyes with ROP and rarely cause postoperative macular displacement [2–5].

The indication of early vitrectomy is mainly the presence of zone 1 or posterior zone 2 ROP with progression of the ROP even after PC. However, there may be some patients with moderate ROP who have a peripheral retinal detachment caused by active vascular proliferation. In these cases, SB reduces the traction caused by the proliferative membranes which results in a decrease of the proliferative activity. In addition, supplemental PC applied on the dried retina after SB can lead to a resolution of the retinopathy in some of eyes.

It has recently been shown that the vascular endothelial growth factor (VEGF) produced from the avascular area of the retina was the main cause for the development and progression of ROP [6]. In addition, it is reported that an intravitreal injection of bevacizumab, an anti-VEGF antibody, decreases the intraocular concentration of VEGF, resulting in an improvement of the retinopathy [7]. However, it has not been determined whether additional treatments by PC and/or IVB will be more effective than SB alone.

The purpose of this study was to determine whether an encircling SB in eyes with stages 4A and 4B ROP combined with PC and/or IVB is better for retinal reattachment than SB alone. The anatomical success rates after the initial surgery and after the final treatments were compared to those in the SB alone group.

Patients and methods

Patients

The medical records of 42 consecutive eyes of 28 patients (20 boys and 8 girls) with stage 4 ROP that had been treated with encircling SB surgery, (the main surgical procedure for stage 4 ROP except for cases with vitreous hemorrhage at the Nagoya University Hospital), between February 2006 and September 2012 were reviewed. Twenty-nine eyes had stage 4A ROP and 13 eyes had stage 4B ROP. None of the eyes had the most severe form of ROP with aggressive posterior ROP.

The mean body weight at birth was 843 ± 258 g (± standard deviation) with a range of 494–2130 g. The mean gestational age at birth was 25.3 ± 2.2 weeks with a range of 22–31 weeks. PC had been performed on all patients at the original hospital before they were referred to our hospital.

At the time of referral, the mean postmenstrual age was 39.3 ± 5.0 weeks with a range of 23 weeks and 5 days to 54 weeks and 6 days, and the mean body weight was 2626.5 ± 862.3 g with a range of 1082–5640 g. At the time of surgery, the mean postmenstrual age was 41.6 ± 4.1 weeks with a range of 34–64 weeks, and the mean body weight was 2706 ± 888 g with a range of 1082–5640 g. The mean follow-up period was 49 ± 19 months with a range of 6–88 months.

Surgical methods

Whenever the results of our first examination of the infants showed that the PC was insufficient, PC was performed before any other treatment, including buckling surgery. Encircling scleral buckling (SB) surgery was performed on 26 eyes, segmental SB on 9 eyes, and combined encircling and segmental SB on 7 eyes as the initial surgery. Segmental SB surgery was performed as an additional surgery in 1 eye. In 17 eyes of 12 patients with 13 stage 4A eyes and 4 stage 4B eyes, encircling and/or segmental SB surgery were combined with additional treatments intraoperatively or postoperatively on an ad hoc basis. These ad hoc treatments were additional PC on 6 stage 4A eyes and 2 stage 4B eyes, IVB on 4 stage 4A eyes and 2 stage 4B eyes, and both PC and IVB in 3 stage 4A eyes. PC was combined with SB as the initial surgery in 7 of 17 eyes, and was performed as additional treatment on 5 eyes. These eyes were placed in the combined group (Table 1). The indications for PC were determined by the size of the remaining avascular areas and also by the vascular activity in the fluorescein angiograms. PC was also performed intraoperatively or postoperatively to the dried retina on the buckle or posterior to the buckle, i.e., on vascularized retinae, and not directly or near the proliferative tissue to avoid creating iatrogenic retinal tears. The indications for IVB were determined by the presence of plus disease that was expected not to be resolved by SB alone, by the presence of hazy fundus due to vitreous hemorrhage, poor mydriasis, and by the need for temporizing before vitrectomy. Some eyes underwent combined SB with a single additional PC or IVB initially but finally had both PC and IVB as a result of ad hoc basis treatment. The use of bevacizumab was approved by the Institutional Review Board of Nagoya University, and a signed written consent form was obtained from each parent of the underaged patients.

The remaining 25 eyes of 17 patients underwent encircling and/or segmental SB procedures without additional treatment and were placed in the non-combined group (Table 2). The indications for vitrectomy as an additional surgery for stage 4A ROP eyes was the absence of decrease in the activity of proliferative tissue after the treatment and an ROP that progressed to stage 4B or stage 5. For stage 4B ROP eyes, the indications were a failure of foveal attachment or the ROP progressed to stage 5. We did not perform vitrectomy for a dragged disc or for retinal folds if the activity of the proliferative tissue had decreased.

Rates of retinal reattachment

The rate of retinal reattachments in the combined groups was compared to that in the non-combined groups for stage 4A and 4B ROP eyes. A failure of retinal reattachment was defined to be when the eye required vitrectomy because of the progression of ROP or foveal retina was detached after surgery.

Table 1 Characteristics of eyes that underwent encircling and/or buckling surgery with additional therapy of intravitreal bevacizumab injection or laser treatment for retinopathy of prematurity

Case no./sex/eye	GA (w)	BW at birth (g)	Zone	Stage	1st surgery	Clock hours	Initial reattachment (Y/N)	PMA at 1st surgery (W)
1/M/OS	22	494	I	4A	Enc + IVB	7–11	Y	34
2/M/OS	23	660	II	4A	Enc + IVB	1–5	Y	35
3/M/OD	22	502	II	4A	Enc + IVB	2–5	Y	37
3/M/OS	22	502	II	4A	Enc + IVB	2–4, 8–10	Y	37
4†/M/OD	27	988	II	4A	SB	8–10	Y	37
5/M/OD	24	611	II	4A	SB + PC	12–4	Y	38
5/M/OS	24	611	II	4A	SB + PC	12–4	Y	38
6/M/OD	27	1220	I	4A	Enc + PC	2–5	Y	38
7/F/OS	22	592	II	4A	Enc + IVB	2–6	Y	39
8/M/OS	25	870	II	4A	Enc + PC	9–12	Y	40
9/M/OS	25	700	II	4A	Enc + PC	7–9	Y	40
10/F/OS	31	1014	II	4A	Enc + IVB	7–10	N	42
11/M/OS	28	1161	II	4A	SB + PC	2–4	Y	42
2/M/OD	23	660	II	4B	Enc + IVB	6–10	Y	35
4†/M/OS	27	988	I	4B	Enc	12–5	Y	37
11/M/OD	28	1161	II	4B	Enc + SB + PC	8–11	Y	42
12/F/OD	23	642	II	4B	Enc + IVB	12–12 (360°)	N	37

Case no./sex/eye	BW at 1st surgery (g)	Additional surgery	VEGF in aqueous humor (pg/ml)	Final VA (decimal/logMAR)	Cerebral palsy	F/U (M)	Final status of affected eye			Status of fellow eye/treatment
							Attachment of fovea	Retinal fold	Peripheral RD	
1/M/OS	1082	IVB⇢PPV	4570	LP	–	30	+	+	+	St 3/PC
2/M/OS	1576	–	N/A	LP	–	6	+	–	–	N/A
3/M/OD	1336	–	N/A	LP	–	15	+	–	–	N/A
3/M/OS	1336	–	N/A	LP	–	15	+	–	–	N/A
4†/M/OD	2254	PC	1750	0.01/2.0	–	69	+	+	+	N/A
5/M/OD	1994	–	1410	0.2/0.7	–	42	+	–	+	N/A
5/M/OS	1994	–	N/A	0.25/0.6	–	42	+	+	+	N/A
6/M/OD	2214	IVB⇢SB	1400	0.4/0.4	–	36	+	+	+	St 3/PC
7/F/OS	1920	PC	564	0.10/1.0	–	68	+	–	–	St 3/PC
8/M/OS	2000	PC	N/A	0.07/1.1	+	36	+	–	+	St 3/PC
9/M/OS	2930	–	1410	0.32/0.5	–	42	+	–	–	St 3/PC
10/F/OS	2620	PC⇢PPL + PPV	2390	0.1/1.0	–	38	+	+	+	St 3/PC
11/M/OS	2730	–	N/A	0.07/1.1	–	27	+	–	–	N/A

Table 1 continued

Case no./sex/eye	BW at 1st surgery (g)	Additional surgery	VEGF in aqueous humor (pg/ml)	Final VA (decimal/logMAR)	Cerebral palsy	F/U (M)	Final status of affected eye			Status of fellow eye/treatment
							Attachment of fovea	Retinal fold	Peripheral RD	
2/M/OD	1576	–	N/A	LP	–	6	+	–	–	N/A
4†/M/OS	2254	PC	1890	0.02/1.7	–	69	+	+	+	N/A
11/M/OD	2730	–	N/A	0.07/1.1	–	27	+	+	+	N/A
12/F/OD	1684	PPV	N/A	LP	–	51	–	+	+	N/A

BW body weight, *Enc* encircling, *F* female, *GA* gestational age, *IVB* intravitreal bevacizumab injection, *LP* light perception, *M* male, *NA* not applicable, *OD* right eye, *OS* left eye, *PC* photocoagulation, *PMA* postmenstrual age, *PPL* pars plicata lensectomy, *PPV* pars plicata vitrectomy, *RD* retinal detachment, *SB* scleral buckling, *VA* visual acuity, *VEGF* vascular endothelial growth factor

† This case was reported in ref. No. 9

Extent of proliferative tissue

The extent of the proliferative tissue is shown in clock hours in Tables 1 and 2, and was categorized as less than one quadrant, 1–2 quadrants, and more than 2 quadrants. The number of eyes in the combined and the non-combined groups according to this categorization is shown in Table 3.

Vascular endothelial growth factor concentration in aqueous humor

To prevent an elevation of the intraocular pressure resulting from surgical procedures, aqueous humor was withdrawn prior to the surgery. The VEGF concentration in the aqueous humor was measured in 8 eyes of the combined group and in 10 eyes of the non-combined group. Cases that had their VEGF measured were randomly selected, and some of the cases were excluded because the amount of aqueous humor withdrawn was too small to be analyzed. The aqueous samples were stored at −80 °C until the concentration of VEGF was determined by enzyme-linked immunosorbent assay using a commercially available kit (Quantikine: R&D Systems Inc., Minneapolis, MN, USA). This kit measures both human VEGF121 and VEGF165, and the detection range of the assay was 31.3–2000 pg/ml. The measurement of the VEGF concentration in the aqueous humor was approved by the Institutional Review Board of Nagoya University, and a signed written consent form was obtained from each parent of the young patients.

Surgical procedures

A #506 buckle (MIRA Inc., Waltham, MA, USA) was used for the segmental SB surgery, and a #40 encircling band (MIRA Inc.) was used for the encircling procedure. The buckle was sutured at the position of the traction by the proliferative membranes. Additional PC was applied either intraoperatively or postoperatively to the dried retina on the buckle or posterior to the buckle, and not directly or near the proliferative tissue to avoid iatrogenic retinal tears.

For the IVB injections, aqueous humor was removed to prevent an elevation of the intraocular pressure before 0.75 mg/0.03 ml of bevacizumab was injected into the mid-vitreous using a 30G needle inserted 1 mm posterior to the corneal limbus.

Statistical analyses

Statistical analyses were performed using Statcel 3 software (Microsoft Corp. Redmond, Washington, USA). The differences between the mean postmenstrual age at birth, the mean body weight at birth, the mean postmenstrual age

Table 2 Characteristics of eyes that underwent encircling and/or buckling for retinopathy of prematurity

Case no./sex/eye	GA (w)	BW at birth (g)	Zone	Stage	1st surgery	Clock hours	Initial reattachment (Y/N)	PMA at 1st surgery (W)
13/F/OS	28	2130	I	4A	SB + Enc	2–5	Y	38
14/F/OS	23	597	II	4A	Enc	6–9	Y	39
15/M/OD	23	596	II	4A	SB	8–10	Y	40
15/M/OS	23	596	II	4A	SB + Enc	8–10	Y	40
16/M/OD	25	709	II	4A	Enc + SB	1–4	Y	41
16/M/OS	25	709	II	4A	Enc	7–10	Y	41
17/M/OD	27	1116	II	4A	Enc	6–8, 2–4	Y	41
17/M/OS	27	1116	I	4A	Enc	8–11	Y	41
18/M/OS	25	692	II	4A	Enc	12–6	Y	42
19/M/OS	29	1628	II	4A	SB	2–4	Y	45
20/F/OD	26	812	II	4A	Enc	6–11	Y	46
20/F/OS	26	812	II	4A	SB	2–4	Y	46
21/M/OD	24	622	II	4A	Enc	6–9	Y	46
22/M/OD	22	528	I	4A	SB	6–9	N	47
23/M/OD	23	633	II	4A	SB + Enc	7–12	Y	48
24/M/OD	29	1228	II	4A	SB + Enc	6–11, 2–4	Y	51
12/F/OS	23	642	II	4B	Enc	1–6	N	37
14/F/OD	23	597	II	4B	Enc	4–9	N	39
19/M/OD	29	1628	II	4B	Enc	5–12	N	39
21/M/OS	24	622	II	4B	Enc	2–5	N	46
25/F/OD	28	952	II	4B	Enc	7–11	N	40
25/F/OS	28	952	II	4B	Enc	1–4	N	40
26/F/OD	30	1196	II	4B	Enc	7–11	Y	45
27/M/OD	24	630	II	4B	SB + Enc	8–11	Y	60
28/M/OS	24	654	II	4B	SB	7–11	Y	64

Case no./sex/eye	BW at 1st surgery (g)	Aditional surgery	VEGF in aqueous humor (pg/mL)	Final VA (decimal/ logMAR)	Cerebral palsy	F/U (M)	Final status of affected eye			Status of fellow eye/treatment
							Attached fovea	Retinal fold	Peripheral RD	
13/F/OS	1526	–	N/A	0.1/0.6	–	75	+	+	+	St 3/PC
14/F/OS	1292	–	1180	LP	–	55	+	+	+	N/A
15/M/OD	2662	–	672	0.8/0.1	–	51	+	–	–	N/A
15/M/OS	2662	–	696	0.05/1.3	–	51	+	+	+	N/A
16/M/OD	2510	–	755	0.02/1.7	–	29	+	+	+	N/A

Table 2 continued

Case no./sex/eye	BW at 1st surgery (g)	Aditional surgery	VEGF in aqueous humor (pg/mL)	Final VA (decimal/logMAR)	Cerebral palsy	F/U (M)	Final status of affected eye			Status of fellow eye/treatment
							Attached fovea	Retinal fold	Peripheral RD	
16/M/OS	2510	–	1170	0.02/1.7	−	29	+	+	+	N/A
17/M/OD	3000	–	832	0.07/1.1	+	29	+	+	−	N/A
17/M/OS	3000	–	1510	LP	+	29	+	−	+	N/A
18/M/OS	2864	–	N/A	LP	+	53	+	−	+	St 3/PC
19/M/OS	5030	–	N/A	0.05/1.3	−	74	+	+	+	N/A
20/F/OD	3855	–	N/A	0.13/0.9	−	78	+	−	−	N/A
20/F/OS	3855	–	N/A	0.13/0.9	−	78	+	−	−	N/A
21/M/OD	4710	–	N/A	0.1/1.0	−	29	+	−	−	N/A
22/M/OD	1972	PPL + PPV	N/A	LP	+	88	+	−	−	St 5/Vitrectomy
23/M/OD	3355	–	1010	LP	−	51	+	−	+	St 3/PC
24/M/OD	5640	–	N/A	LP	+	84	+	+	+	St 3/PC
12/F/OS	1684	PPL + PPV	1570	LP	−	51	−	+	+	N/A
14/F/OD	1292	PPV	455	LP	−	55	+	+	+	N/A
19/M/OD	3600	PPL + PPV	N/A	LP	−	48	+	+	+	N/A
21/M/OS	4710	PPL + PPV	N/A	LP	−	29	+	+	+	N/A
25/F/OD	2530	PPL + PPV	N/A	LP	−	79	+	+	+	N/A
25/F/OS	2530	PPL + PPV	N/A	LP	−	79	+	+	+	N/A
26/F/OD	3640	–	N/A	LP	−	74	+	+	+	St 3/PC
27/M/OD	4216	–	N/A	LP	−	81	+	+	+	St 3/PC
28/M/OS	4808	–	N/A	0.16/0.8	−	77	+	+	+	St 3/PC

BW body weight, *Enc* encircling, *F* female, *GA* gestational age, *IVB* intravitreal bevacizumab injection, *LP* light perception, *M* male, *NA* not applicable, *OD* right eye, *OS* left eye, *PC* photocoagulation, *PMA* postmenstrual age, *PPL* pars plicata lensectomy, *PPV* pars plicata vitrectomy, *RD* retinal detachment, *SB* scleral buckling, *VA* visual acuity, *VEGF* vascular endothelial growth factor

† This case was reported in ref. No. 9

Table 3 The number of eyes categorized according to the number of quadrants of proliferative tissue in each group

Number of quadrants of proliferative tissue	Combined		Non-combined	
	Stage 4A	Stage 4B	Stage 4A	Stage 4B
1≧	7	1	11	3
1–2	6	2	3	5
2≦	0	1	2	1

at the initial surgery, and the differences of the mean VEGF concentrations in the aqueous humor between the 2 groups and also between the combined group and non-combined group were analyzed by Mann–Whitney U tests. A P value <0.05 was considered to be statistically significant.

Results

Demographics of patients

The mean postmenstrual age at birth was 25.5 ± 2.1 weeks in the non-combined group and 25.0 ± 2.0 weeks in the combined group ($P = 0.53$). The mean body weight at birth was 899 ± 315 g in the non-combined group and 786 ± 222 g in the combined group ($P = 0.85$). The mean postmenstrual age at the time of the initial surgery in the combined group was 38.0 ± 1.9 weeks which was significantly younger than that of the non-combined group (44.1 ± 4.0 weeks; $P < 0.001$).

Extent of proliferative tissues

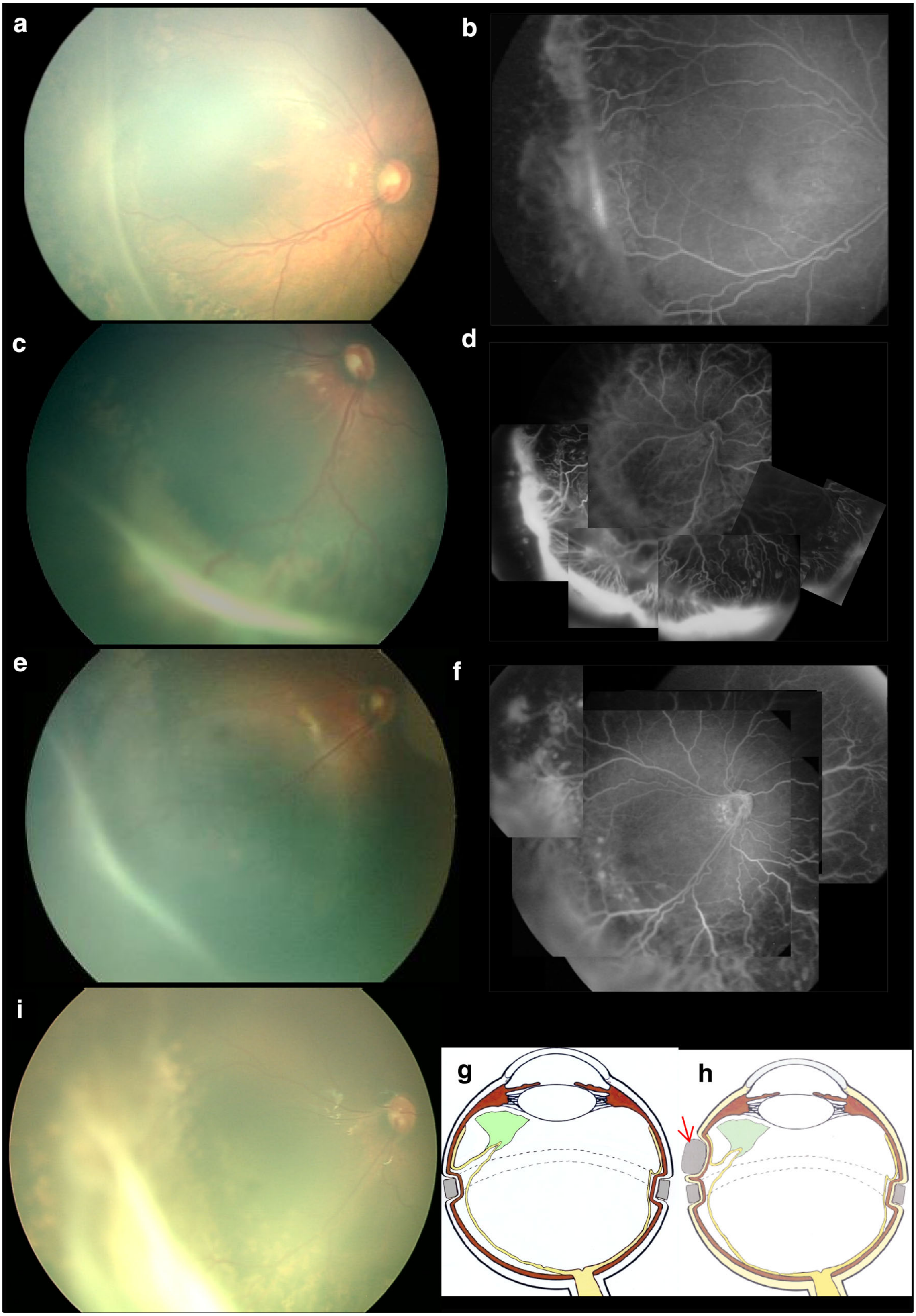
The number of stage 4A ROP eyes with proliferative tissue ≦1 quadrant was 7 in the combined group and 11 in the non-combined group, and the number of eyes with 1–2 quadrants was 6 in the combined group and 3 in the non-combined group. Thus, the size of the proliferative tissue was larger in the combined group than in the non-combined group.

Rates of retinal reattachment

In the combined group (Table 1), the initial reattachment rate was 92 % (12/13 eyes) for stage 4A ROP and 75 % (3/4) for stage 4B ROP. The 3 eyes with stage 4A ROP (cases 1, 6 and 10) required additional surgery (Table 1). In case 1, the eye progressed to total detachment 6 months after an initial reattachment and the fovea was finally reattached by IVB and PPV. In case 6, additional treatment with IVB was required due to persistent ROP activity after the initial retinal reattachment with encircling and PC. However, SB was used to treat the subsequent progression to stage 4B after the IVB injection, resulting in a final retinal reattachment. Case 10 underwent vitreous surgery as an additional surgery because no initial reattachment was achieved with encircling SB and IVB injection and even with an additional PC. In addition, vitrectomy was performed because the case progressed to stage 4B ROP. This case was treated with pars plicata lensectomy (PPL) and PPV, and the foveal retina was finally reattached with peripheral retina detached. The fovea of stage 4B ROP eyes with almost 360° of proliferative tissue (case 12) was not reattached after the initial encircling SB and IVB injection, and the retinopathy progressed to stage 5 ROP. In this case, the foveal detachment persisted even after additional vitreous surgery. Thus, the final reattachment rate was 100 % for stage 4A eyes (13/13 eyes) and 75 % for stage 4B eyes (3/4 eyes). Finally, all eyes with stage 4A ROP in the combined group (Table 1) achieved foveal attachment, 5 eyes of the 13 eyes had retinal folds, and 7 eyes of the 13 eyes had a residual peripheral retinal detachment. In addition, 3 of 4 stage 4B ROP eyes in the combined group achieved foveal attachment, but 3 of the 4 eyes had retinal folds and 3 of the 4 eyes had persistent peripheral retinal detachment.

In the non-combined group (Table 2), the initial reattachment rate was 93 % (15/16 eyes) in stage 4A ROP eyes and 33 % (3/9) in stage 4B ROP eyes. Vitrectomy was required in one eye that did not have a reattachment with segmental SB alone (case 22), because the ROP had progressed to stage 5. Retinal reattachment was finally achieved after the vitrectomy. One eye at stage 4A ROP that had an initial retinal attachment with encircling and buckling procedures (case 24) progressed to total retinal detachment after 4 years. Because this eye had no light perception, the parents chose not to have their child undergo another surgery. Therefore, this eye was classified as a failure of reattachment. The final reattachment rate in eyes with stage 4A ROP was 93 % (15/16 eyes).

For 6 stage 4B ROP eyes in which no foveal reattachment was achieved after the initial surgery, 5 eyes achieved foveal retinal reattachment after PPV. In the remaining eye (case 14), vitreous surgery failed to attach the detached retina after unsuccessful initial encircling SB surgery. The final reattachment rate in eyes with stage 4B ROP was 88 % (8/9 eyes). In the end, all eyes with stage 4A ROP in the non-combined group (Table 2) achieved foveal attachment, but 8 eyes of the 16 eyes had retinal folds, and 10 eyes had residual peripheral retinal detachment. Eight out of 9 stage 4B ROP eyes in the combined group achieved foveal attachment, and all 9 eyes had retinal folds and persistent peripheral retinal detachment.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◀**Fig. 1** Representative case that required combined surgery (case 6, Table 1). Right eye of a boy born at a gestational age of 27/0 weeks (week/day) with a body weight of 1220 g that developed a ROP at a postmenstrual age of 31 weeks and was treated with PC. The patient was referred to our hospital at 38/1 weeks because of the extension of the proliferative membrane to the posterior surface of the lens. **a** At the initial examination at 38/1 weeks, the right eye was at stage 4A ROP with a vascular membrane on the temporal side. **b** Fluorescein angiogram at the initial examination showed active leakage from the vascular membrane. **c** At 41/4 weeks, the vascular activity was high after a transient vascular regression after the initial surgery by encircling SB with photocoagulation (PC) at 38/5 weeks. **d** Fluorescein angiography at 41/4 weeks showed severe vascular leakage from the proliferative membrane. **e** One week after the IVB injection, the fundus photograph showed that the activity of the proliferative membrane was decreased at 42/5 weeks. **f** Fluorescein angiography at 42/5 weeks showed a decreased vascular leakage. **g** Schematic drawing demonstrates a stage 4B ROP with a fibrovascular membrane dragging the retina toward the posterior lens capsule which progressed 1 week after a transient decrease of vascular activity by IVB injection. **h** Schematic drawing showing that a local scleral buckle was added on the peripheral side of the encircling band (*red arrow*) to reduce the traction. At 55/4 weeks, the macula was reattached. **i** After an additional SB, the posterior retina was reattached at 55/4 weeks

VEGF concentration in aqueous humor

The mean VEGF concentration in the aqueous humor in the 18 eyes at the time of encircling and/or segmental SB was 1402 ± 587 pg/ml with a range of 455–4570 pg/ml. The mean VEGF concentration in the 8 eyes in the combined group was 1923 ± 779 pg/ml which was significantly higher than that in 10 eyes in the non-combined group at 985 ± 303 pg/ml ($P < 0.05$).

Cases 1 and 10 in stage 4A eyes in the combined group (Table 1) required additional vitreous surgery; these eyes had high VEGF concentrations in the aqueous humor of 4570 pg/ml (case 1) and 2390 pg/ml (case 10) at the time of the initial surgery reflecting the high ROP activity. They received IVB injections at the initial surgery as a combined therapy, and the VEGF concentrations in the aqueous humor at the time of the additional surgeries decreased to 470 pg/ml in case 1 and 1320 pg/ml in case 10, (data not shown). This occurred even with the proliferative tissue appearing active.

Case report (case 6 in Table 1)

The findings in a representative case are shown in Fig. 1 (see also Table 1). This boy was born at a gestational age of 27/0 weeks (week/day) with a body weight of 1220 g. The right eye developed ROP at a postmenstrual age of 31 weeks and was treated with photocoagulation (PC). The patient was referred to our hospital at 38/1 weeks because of the extension of the proliferative membrane to the posterior surface of the lens.

At the initial examination, the right eye was at stage 4A ROP with a vascular membrane on the temporal side (Fig. 1a). Fluorescein angiography showed active leakage from the vascular membrane (Fig. 1b). At 38/5 weeks, encircling SB surgery with PC was performed. The VEGF concentration in the aqueous humor removed immediately before surgery was 1400 pg/ml. At 39/0 weeks, additional PC was applied due to a persistent vascular activity and an extended circumferential proliferative membrane. At 41/4 weeks, IVB was injected because of aggravated vascular activity after a transient vascular regression after the surgery (Fig. 1c, d). The VEGF concentration in the aqueous humor remained high at 880 pg/ml. One week after the IVB injection (42/5 weeks), the activity of the proliferative membranes decreased (Fig. 1e, f); however, the disease progressed to stage 4B because of the contraction of the fibrovascular membrane between the edge of the proliferation and the posterior lens capsule (Fig. 1g). At 44/6 weeks, a focal scleral buckle was added on the temporal and peripheral side of the encircling band (*arrow*; Fig. 1h) to reduce the traction. The VEGF concentration in the aqueous humor at this time was below the detection limit. At 55/4 weeks, the posterior retina was reattached (Fig. 1h, i).

Discussion

Our results show that the anatomical success rates in stage 4A ROP eyes undergoing combined scleral buckling and IVB and/or PC, and in eyes in the non-combined group that underwent only scleral buckling were comparable. The comparable rates were found in spite of the fact that the retinopathy was more severe in the stage 4A ROP eyes in the combined group because the proliferative tissue in this group was larger at the time of initial surgery. In addition, the VEGF concentration in the aqueous humor in the combined group was higher. This suggests that the combined surgery had some positive effect on the results of the treatment.

Hartnett et al. [3] compared the results of SB surgery and lens-sparing vitrectomy in eyes at stage 4 ROP. They report that although the rate of retinal reattachment at 1 month after the initial surgery with lens-sparing vitrectomy was 72 %, significantly higher than that with SB alone (31 %), the reattachment rate at 6 months for lens-sparing vitrectomy after several sessions of surgery was 82 %: not significantly different from that for SB alone (69 %). Hinz et al. [8] report that the reattachment rate was 75 % (6/8) in eyes at stage 4A ROP treated with SB as the initial surgery. Our results indicate that the initial reattachment rates for eyes at stage 4 ROP (sum for eyes at stage 4A ROP and stage 4B ROP in each group) was

88.2 % (15/17) in the combined group and 72.0 % (18/25) for eyes in the non-combined group. These rates are also comparable to those for lens-sparing vitrectomy alone (72 %) reported by Hartnett et al.

Retinal photocoagulation is a standard method for reducing the activity of ROP [9, 10]. When the vascular activity increases, leading to retinal detachments even after sufficient application of PC, the detached retina will increase the vascular activity. Hinz et al. [8] state that reattaching a detached retina by SB and relieving the traction of the proliferative membrane were effective in reducing the vascular activity. Additional PCs can be applied where the subretinal fluid was drained by the indentation with SB. In some combined group patients, the intraoperative and/or postoperative PC application combined with SB also reduced the activity of the retinopathy. A question arose whether adding PC would help when PC had been performed inadequately prior to the SB surgery, or if adding PC was efficacious regardless of how adequately the PC had been performed. All of the cases had received PC in the avascular area in the referring hospitals, and whenever we judged that the PC was insufficient, it was given as soon as the patients were admitted to our hospital, before buckling surgery. The additional PC was applied either intraoperatively or postoperatively to the dried retina on the buckle or posterior to the buckle, i.e. the vascularized retina. We believe that the effectiveness of adding PC in eyes that had achieved a resolution only with buckling and PC was due to the ablation of the dried retina on the buckle or posterior to the buckle.

Vitreous surgery was finally required in 3 of 17 eyes in the combined group. We suggest that this was because SB could not eliminate the traction in these cases, and the proliferative activity would not have decreased unless the traction was completely relieved. Thus, when the activity of retinopathy is not reduced despite the combined therapy, vitreous surgery needs to be considered.

It is reasonable to believe that the eyes in the combined group had higher activity of the proliferative membrane because the proliferative tissue was larger at the time of the initial surgery. In addition, the VEGF concentration in the aqueous humor was higher in the combined group than in the non-combined group. Therefore, the retinal reattachment rate in the combined group was expected to be lower than in the non-combined group. However, the combined treatment by IVB and/or PC with SB reduced the activity of retinopathy and VEGF concentration in aqueous humor. These changes led to a retinal reattachment rate equivalent to that in the non-combined group.

The VEGF concentrations in the aqueous humor and vitreous body are greatly increased in eyes with ROP [7, 11]. It is reported that IVB will decrease the VEGF concentration in the vitreous body, resulting in a reduction of the retinopathy activity. Recently, a prospective, controlled, randomized multicenter trial [12] was conducted to investigate the recurrence rates of retinopathy in eyes with stage 3 + and more severe ROPs between treatments with IVB monotherapy and with conventional PC. The authors report that the recurrence rate was significantly lower, especially in eyes with zone I, in eyes treated with IVB monotherapy. In our study, SB was combined with IVB in 8 eyes in the combined group because their clinical findings suggested that SB alone would not decrease the activity of the proliferative membrane. In addition, IVB was injected in an eye with persistent high activity of the proliferative membrane after the initial encircling SB surgery (case 6; Table 1), and this eye required additional SB surgery. The progression of the ROP in case 6 was probably due to a contraction of the fibrovascular membrane, a complication caused by the IVB injection. Kusaka et al. [5] report that tractional retinal detachment occurred or was aggravated in 3 of 23 eyes with ROP treated with IVB injection alone. Because IVB injection can cause this complication, it is reasonable to reduce the traction of the proliferative membrane with SB combined with IVB. In all cases, care must be taken when IVB is used in eyes with advanced ROP such as stage 4B ROP. Furthermore, as it is reported that intraocular administration of bevacizumab can enter the systemic circulation and decrease serum VEGF concentration [13], further investigations are required on its use.

We reported the surgical results in eyes that had prior segmental and/or encircling SB surgery, but not including eyes that underwent vitreous surgery. SB used to be the most common procedure for stage 4 ROP [8]; however, the effectiveness of lens-sparing vitrectomy has recently been reported [2–4]. In addition, vitreous surgery at an early stage was also introduced for cases of aggressive posterior ROP [14]. However, SB surgery may be better than vitreous surgery in eyes with proliferation in the peripheral retina that extends toward the posterior lens because lensectomy is necessary to remove the traction. This could then lead to ametropic amblyopia postoperatively, even with adequate pleoptics.

This study was not designed to investigate the surgical results of aggressive posterior ROPs, and neither the combined nor the non-combined group contained a case of aggressive posterior ROP. However, early vitreous surgery is reported to be effective [14], and the proliferative membranes were too posterior for the buckle to be effective.

The number of cases with stage 4B ROP in the 2 groups was uneven: 4 eyes in the combined group and 9 eyes in the non-combined group. This was a retrospective study, and it was difficult to equalize the number of cases in the 2 groups. This difference made it difficult to compare the results and is a limitation of this study. In addition, we grouped the cases treated with three different additional therapies, PC, IVB, and PC with IVB in the same combined group, and the number of the cases for each therapy was relatively small. The effects of IVB and PC on ROP are essentially different because IVB would have an adverse effect on the traction on the retina and seems to be contraindicated in advanced ROP. It is difficult to conclude the effectiveness of the combined therapy. This is a limitation of this study.

In conclusion, the rate of retinal reattachment after combined therapy was comparable to that in the non-combined group, even though the activity of the proliferation was significantly higher because of the larger proliferative membranes and higher VEGF concentrations. In eyes with proliferative membranes with high activity, combined therapy with IVB or PC as the initial surgery may be effective. Even when SB alone fails to resolve the activity of ROP, additional IVB or PC on the reattached retina may decrease the activity of the disease.

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