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Prostaglandin levels in human vitreous

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SUMMARY Vitreous samples were obtained from 41 eyes undergoing vitrectomy, and radioimmunoassays were performed to measure concentrations of the prostaglandins PGE_2, $PGF_{2\alpha}$, prostacyclin, and thromboxane. Presumably physiological levels (approximately 100 picograms/ml) were found in vitreous from eyes undergoing cataract extraction. Eyes with vitreous haemorrhage, retinal detachment, or cystoid macular oedema had similarly low levels. Vitreous prostaglandins were mildly elevated in trauma and endophthalmitis and markedly elevated in aphakic bullous keratopathy. The role prostaglandins may play in cystoid macular oedema is reviewed.

Prostaglandins are important mediators of inflammation, and the synthesis of these vasoactive prostaglandin compounds (PGE_2, $PGF_2\alpha$, prostacyclin [PGI_2]) by ocular tissues has been demonstrated. Low levels of these prostaglandins are found in normal human aqueous. A variety of conditions in which anterior chamber inflammation is present (keratitis, paracentesis, panretinal photocoagulation, etc.) have higher aqueous levels.[1-4] Elevated aqueous levels have also been found in association with aphakic cystoid macular oedema. Several investigators believe that prostaglandins synthesised in the anterior segment (as in iris and ciliary body) diffuse through the vitreous and then act on retinal capillaries to produce macular oedema.[5,6] Miyake, Yannuzzi, Klein, and others have reported clinical trials in which a topical or oral prostaglandin inhibitor, indomethacin, given preoperatively and in the early postoperative period was associated with a lower incidence of fluorescein angiographic aphakic cystoid macular oedema.[7-11] Miyake also noted concurrent reduction in aqueous prostaglandin levels and clinical improvement in the cystoid macular oedema. Furthermore, Miyake *et al.* have reported [12] elevated aqueous prostaglandins in eyes which developed cystoid macular oedema after intracapsular cataract extraction with vitreous loss and vitreous incarceration to the wound. Pars plana vitrectomy led to lower aqueous prostaglandins and improvement in the oedema of relatively short duration.[12]

Despite extensive speculation that prostaglandins, which are synthesised anteriorly, pass through the vitreous and play a pathological role in the posterior pole, concentrations of prostaglandins in the vitreous itself have not been reported either in normal or in diseased eyes. We have therefore measured vitreous prostaglandin levels in 41 eyes, two of which had cystoid macular oedema, and have identified factors possibly associated with elevated vitreous prostaglandins.

Materials and methods

Vitreous specimens were obtained during intraocular surgery on 41 eyes. In six cases vitreous presentation occurred during cataract extraction, thus necessitating an anterior vitrectomy. Fifteen eyes had vitreous haemorrhage. Six had retinal detachment without vitreous haemorrhage, five had aphakic bullous keratopathy (ABK), for which penetrating keratoplasties and anterior vitrectomies were performed; three had trauma, two had cystoid macular oedema, one had endophthalmitis, and three had miscellaneous indications for vitrectomy. To allow accurate determination of prostaglandin concentration we attempted to remove specimens from the eye before dilution by balanced salt solution (BSS) infusion occurred. In the 18 anterior vitrectomies (44% of the total), this was accomplished by an 'open sky' tech-

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nique. With the cornea retracted, the VISC-10 vitrectomy instrument tip was placed directly in formed vitreous and the specimen was cut, aspirated, and removed from the system before any infusion was begun. In the 24 pars plana vitrectomies (56% of the total) the VISC-10 tip was directly visualised through the pupillary space in formed vitreous. An initial sample (usually about $1cm^3$) was cut, aspirated, and removed from the system prior to starting BSS infusion. In each case the vitrectomy instrument was in view at all times and was cutting without exerting traction on the vitreous base. As vitreous volume decreased, slight scleral infolding was occasionally observed, but no intraoperative damage to the retina or lens was seen in any of the cases. Infusion was begun immediately if there was any question of tractional forces on the retina. In only seven of the 41 cases was infusion necessary before the specimen was obtained. In these cases the surgeon estimated the percentage dilution at the time of the procedure.

To minimise artefactual prostaglandin synthesis the vitreous was immediately transferred into tubes containing 0·5 ml (10 μg) of indomethacin. The tubes were kept on ice, centrifuged for 10 minutes at 4000 rpm to remove cellular debris, and then stored at −70°C until assays could be performed. Prostaglandins (PG) were measured by the double antibody radioimmunoassay technique of Levine[13] with modifications.[14] Briefly, antisera were raised against each PG by immunising rabbits with PGE_2, $PGF_2\alpha$, 6-keto-$PGF_1\alpha$ (the chemically stable transformation product of PGI_2) and TXB_2 (the chemically stable product of thromboxane A_2) coupled to human serum albumin. 0·1 ml of vitreous fluid was added to 100 μl rabbit anti-PG antibody (in 0·1 M Tris buffer, pH 7·4) and 100 μl tritiated PG. The mixture was incubated at 37°C for one hour. 0·1 ml of normal rabbit serum (1:25 dilution) and 100 μl goat anti-rabbit globulin (1:8 dilution) were then added. After thoroughly mixing the reaction mixture was incubated at 4°C overnight. The antibody-bound tritiated PG was sedimented by centrifugation, the supernatant was discarded, and the precipitate was counted for radioactivity.

There was less than 1% cross-reactivity between the PGE_2 antibody and $PGF_{2\alpha}$, 6-keto-$PGF_{1\alpha}$, and TXB_2; between the $PGF_{2\alpha}$ antibody and PGE_2, 6-keto-$PGF_{1\alpha}$, and TXB_2; or between the TXB_2 antibody and PGE_2, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$. The lowest limit of sensitivity of these assays was 10 pg/ml, and the intra-assay coefficient of variation was less than 10%.

To evaluate further the validity and accuracy of these radioimmunoassay techniques, 6-keto-$PGF_1\alpha$ was added to eight samples. Analysis of these specimens by radioimmunoassay showed a recovery of 101±7%.[15] Similarly, assays performed before and after the addition of PGE_2 showed a recovery of 75±19%. In addition plasma levels of prostaglandins measured by the radioimmunoassay procedures described above are similar to those determined by gas chromatography/mass spectrophotometry.[16]

Results

A brief clinical description of the cases and prostaglandin concentrations are listed in Table 1. Table 2 gives the mean prostaglandin levels for each group of cases. Ages ranged from 28 to 88 years with 70% between 60 and 79. Thirty-seven were men, four were women. Thirty-five of the 41 were Caucasian. Preoperatively visual acuity was less than 20/200 in 30 of the eyes (73%). Twenty-seven (66%) were phakic, 14 (34%) aphakic. Fifteen eyes (37%) had conjunctival injection and/or anterior chamber reaction as evidence of anterior segment inflammation (graded 0 to 4+ in Table 1.) Follow-up was greater than six months in 20 eyes, three to six months for 12 eyes, and for nine eyes the patient was either lost to follow-up or died within three months. Visual acuity improved or remained the same in 31 eyes, decreased in five eyes and five eyes were lost to follow-up. Postoperatively three eyes had slight progression of pre-existing cataracts (nuclear sclerosis); no new cataracts developed. Three eyes developed recurrent retinal detachments; no postoperative detachments occurred in previously attached retinas.

It is not surprising that quiet eyes undergoing routine cataract extraction had very low, presumably physiological, concentrations of vitreous prostaglandins. The levels found in these vitreous samples corresponded well with previously reported normal aqueous levels (around 100 pg/ml).

Neither vitreous haemorrhage nor the presence of a retinal detachment produced prostaglandins in any greater concentration than in the cataract patients. Since there was no appreciable inflammation in these eyes, the low levels are what would be expected.

In three of the five ABK eyes PGE_2 levels were greater than 1000 pg/ml with a mean value of 2569 pg/ml. It is unknown whether prostaglandins may play a causative role in such cases of corneal decompensation or whether elevated levels are coincidental. It is known that principal sites of PGE_2 synthesis are the iris and ciliary body. In the case with the highest level (10 000 pg/ml) dense vitreous adhesions to the iris and Copeland intraocular lens were present. Traction by vitreous strands on the iris/ciliary body may thus have stimulated prostaglandin synthesis.

One of the miscellaneous cases with synechiae

Table 1 *Vitreous prostaglandin levels*

Case	*Age*	*Sex*	*Diagnosis**	*Vision*	*Phakic*	*Inflam.*	*Procedure†*	*Final‡ VA*	PGE_2	$PGF_{2\alpha}$	*6-keto-* $PG_{2\alpha}$	*TX*
Cataracts												
1§	58	M	Cataract	20/200	Yes	0	ICCE, ant. vit.	20/30	0	0	0	0
2	84	M	Cataract	20/200	Yes	0	ICCE, ant. vit.	20/60	0	275	92	0
3	48	M	Cataract	20/80	Yes	0	ECCE, ant. vit.	20/30	332	262	—	—
4	58	M	Cataract, subluxed	20/400	Yes	0	ICCE, ant. vit.	20/30	0	0	0	—
5	59	M	Cataract, subluxed	20/400	Yes	0	ICCE, ant. vit.	LP	142	109	0	—
6	68	M	Cataract	20/200	Yes	0	ECCE, ant. vit.	20/25	373	778	156	—
Vit. Haem.												
7	58	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	20/200	0	285	61	0
8	52	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	HM	0	450	0	42
9	53	M	Vit. haem., RD, PDR	1/200	Yes	0	PPV	LP	0	0	102	—
10§	56	M	Vit. haem., RD, PDR	CF 2 feet	Yes	0	PPV	CF 3 feet	0	0	—	—
11§	49	M	Vit. haem., RD, PDR	HM 1 foot	Yes	0	PPV	Died	0	0	0	0
12	52	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	NLP	0	0	—	—
13	57	M	Vit. haem., PDR	CF	No	0	PPV	LP	0	45	0	—
14	67	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	10/100	75	18	15	—
15	54	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	LP	180	234	0	—
16	65	M	Vit. haem., RD, PDR	LP	Yes	2+	Ant. vit.	LTF	135	120	0	—
17	62	M	Vit. haem., cat., PDR	HM	Yes	0	Ant. vit.	CF 4 feet	480	88	0	—
18‖		M	Vit. haem., RD, PDR	LP	Yes	3+	PPV, ICCE	20/200	281	31	225	—
19		M	Vit. haem., RD, PDR	LP	No	3+	Air-fluid exch.	20/200	0	0	0	—
20	57	M	Vit. haem., PDR	CF	Yes	0	PPV	CF 1 foot exp.	67	1800	0	—
21	65	M	Vit. haem., SMCD	CF	Yes	0	PPV	Died	406	60	650	—
RD												
22§	57	M	RD	5/200	Yes	0	PPV	20/200	0	0	0	102
23	67	M	RD	CF	No	0	PPV, SBP	20/60	0	53	0	—
24	31	M	RD	LP	Yes	2+	PPV, ICCE, SBP	LP	0	0	—	—
25	56	M	RD	HM	No	2+	PPV	20/400	0	0	0	—
26§	31	M	RD	LP	No	2+	PPV, SBP	LP	0	0	0	—
27	50	F	RD, vit. in AC	20/50	No	1+	PPV, SBP	20/15	105	720	0	—
ABK												
28§	62	M	ABK	20/200	No	1+	PPV	Died	139	0	—	—
29	79	F	ABK	1/200	No	3+	Ant. vit., PK	6/200	10 000	110	1000	—
30	78	M	ABK	2/200	No	1+	Ant. vit., PK	HM 5 feet	1050	520	640	—
31	88	M	ABK	CF	No	0	Ant. vit., PK	CF 2 feet	154	650	49	—
32	67	M	ABK	CF	No	0	Ant. vit., PK	20/200	1500	250	320	—
Trauma												
33	28	M	Intraocular FB	20/60	Yes	3+	PPV, IOFB rem.	20/25	238	—	—	—
34	52	M	Dislocated lens	HM	Yes	4+	Ant. vit. ICCE	20/30	0	0	—	—
35	60	M	Dislocated lens	CF	Yes	0	Ant. vit., ICCE	20/60	1100	1320	2600	—
CMO												
36§	59	F	CMO	20/200	No	0	PPV	20/30	0	0	0	0
37	82	F	CMO, ABK	20/200	No	2+	Ant. vit., PK	20/40	0	0	720	—
Endophthalmitis												
38	30?	M	Fungal endophthal.	20/400	Yes	0	PPV	Died	678	550	0	—
Other												
39	85	M	Cataract, glaucoma	LP	Yes	1+	Ant. vit., ICCE, trabeculectomy	20/200	0	1040	80	—
40	47	M	Loose IOL	20/50	No	2+	Ant. vit., IOL removed	20/25	46	0	0	—
41	85	M	Cat. stuck to vit.	20/80	Yes	0	Ant. vit., ICCE	20/25	34 615	332	1523	—

*Diagnoses: Cataract (cat.), vitreous haemorrhage (vit. haem.), retinal detachment (RD), proliferative diabetic retinopathy (PDR), senile macular choroidal degeneration (SMCD), anterior chamber (AC), aphakic bullous keratopathy (ABK), foreign body (FB), cystoid macular oedema (CMO), intraocular lens (IOL).

†Procedure: Intracapsular cataract extraction (ICCE), anterior vitrectomy (ant. vit.), extracapsular cataract extraction (ECCE), pars plana vitrectomy (PPV), scleral buckling procedure (SBP), penetrating keratoplasty (PK), intraocular foreign body removal (IOFB rem.), intraocular lens (IOL).

‡Final visual acuity: length of follow-up: ≥6 months: cases 1, 2, 3, 4, 5, 7, 9, 10, 12, 13, 14, 15, 17, 22, 23, 25, 33, 34, 37, 39. ≥3 months: cases 6, 8, 18, 19, 27, 30, 31, 32, 35, 36, 40, 41. <3 months or lost to follow-up (LTF): cases 11, 16, 20, 21, 24, 26, 28, 29, 38.

§Specimens diluted at time of collection. Percentage dilution estimated by surgeon.

‖Samples 18 and 19 from same patient.

Visual acuity: CF = counting fingers. HM = hand movements. LP = light perception. LTF = lost to follow-up.

Metric conversion: 1 foot = 30cm.

Table 2 *Mean vitreous prostaglandin levels*

Diagnosis	*PGE_2*	*$PGF_{2\alpha}$*	*6-keto-$PG_{2\alpha}$*	*TX*
Cataracts	141	237	49	0
Vitreous haemorrhage	108	209	81	21
Retinal detachment	17	129	0	102
Aphakic bullous ker.	2568	306	502	—
Trauma	446	660	2600	—
Cystoid macular oedema	0	0	360	0
Endophthalmitis	678	550	0	—
Other	11 553	457	534	0

between the posterior lens capsule and the anterior hyaloid face also had extremely high prostaglandin (PGE_2 34 615 pg/ml, 6-keto-$PG_{1\alpha}$ 1523 pg/ml). Synechial adhesions may have led to traction on the iris and thus stimulated synthesis. The mere presence of vitreous in the anterior chamber (with or without corneal touch) did not substantially raise prostaglandin levels.

In our cases anterior inflammation as indicated by cells or flare or conjunctival injection was not associated with higher vitreous prostaglandin levels. In the one case of confirmed posterior segment inflammation (fungal endophthalmitis in an intravenous drug abuser) vitreous prostaglandins were only moderately elevated.

Of the two cases of cystoid macular oedema one had flagrant oedema associated with vitreous to the wound. Unfortunately this was one of the first specimens obtained, and it was diluted with BSS. In the second case the primary diagnosis was aphakic bullous keratopathy, but mild cystoid macular oedema had been demonstrated on a previous fluorescein angiogram. In both cases prostaglandins were undetectably low.

Discussion

Prostaglandins may well be involved in a variety of fundus disorders. Of all the pathological states in which these compounds are suspected, cystoid macular oedema is one of the most important. The evidence implicating prostaglandins in the aetiology of cystoid macular oedema is two-fold. First, an association between elevated aqueous prostaglandins and cystoid macular oedema has been shown. Miyake reported substantial amounts of PGE and $PGF_{2\alpha}$ (both at concentrations of approximately 13 000 pg/ml) in the aqueous of patients after cataract extraction.[5] Furthermore, he reported marked elevation of PGE and $PGF_{2\alpha}$ in the aqueous of nine eyes which had undergone intracapsular cataract extraction with vitreous loss, vitreous incarceration to the wound, and severe cystoid macular oedema.[12] After pars plana vitrectomy the levels were markedly reduced and fluorescein fundus angiography findings improved in five cases with relatively short duration cystoid macular oedema.

Earlier investigators had shown improvement in cystoid macular oedema by relieving vitreous incarceration to the wound. In the 1960s Iliff described a procedure to cut and remove vitreous strands that were anchored by adhesions to the cataract wound in patients with macular oedema. Vision improved in eight of his nine patients.[17] Gass and Norton noted inflammation in most eyes with formed vitreous to the wound and thus performed partial, open-sky anterior vitrectomies to reduce the inflammation and improve acuity. Of nine eyes so treated four remained unchanged, but five improved to 20/40 acuity or better within six months.[18] After the introduction of vitrectomy instruments Fung[19] and Federman *et al.*[20] each produced series of patients receiving vitrectomies for angiographically demonstrated cystoid macular oedema. Three quarters of their cases had at least a two-line improvement in acuity. Fung has summarised surgical therapy for chronic aphakic cystoid macular oedema and described the national, prospective, randomised, controlled study currently under way to assess the value of vitrectomy in this condition.[21]

These clinical demonstrations that resolving vitreous incarceration and mechanical iris irritation improves cystoid macular oedema are consistent with the hypothesis that such irritation produces a mediator which in turn produces cystoid macular oedema. That such a mediator is in fact involved, and that it is a prostaglandin, is not yet proved.

The second category of evidence implicating prostaglandins in cystoid macular oedema is the effect of prostaglandin inhibitors (like indomethacin) on the incidence of this condition. In Miyake's series of 25 cases of bilateral extraction of senile cataracts, topical indomethacin in one eye led to decreased incidence and severity of cystoid macular oedema compared with the fellow eye.[8] In Yannuzzi *et al.*'s series 100 patients undergoing cataract extraction received 1% topical indomethacin four times a day for four to six weeks and had significantly less aphakic cystoid macular oedema five weeks postoperatively (18% vs. 36% for controls), but there was no significant difference at 10 weeks.[10] In Klein *et al.*'s series five of 57 cataract patients who received oral indomethacin for four weeks developed cystoid macular oedema compared with 15 of 34 controls without indomethacin.[11] However, Yannuzzi *et al.* found no improvement in chronic cystoid macular oedema treated with oral indomethacin for three weeks.[22] Sholiton *et al.* did not find any significant difference in their series of 20 patients treated with oral indomethacin for six days (four patients

developed cystoid macular oedema) and the control group (five of 22 developed cystoid macular oedema).[23] Jampol has recently reviewed the pharmacological prophylaxis and treatment of cystoid macular oedema.[6] The efficacy of a prostaglandin inhibitor has not yet been unequivocably proved.[24]

CONCLUSION

Prostaglandins in the vitreous cavity may well be significant in posterior segment disease. The evidence linking the compounds with aphakic cystoid macular oedema has been briefly reviewed. The values reported here indicate that prostaglandins are present in low levels in presumably normal vitreous. High levels seem to be associated with vitreous adhesions to iris. The two cases of cystoid macular oedema included here are insufficient to describe definitively the role vitreous prostaglandins play in this important disorder. Measurement of vitreous prostaglandins in additional cases of cystoid macular oedema will help resolve the question.

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