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Advances in the Management of Vitreomacular Traction Syndrome and Macular Hole

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The management of macular holes, with or without retinal detachment, has benefited considerably from the biomicroscopic and histopathologic identification of changes at the vitreomacular interface, as well as from advances in vitreoretinal surgery, generally.

Idiopathic macular holes are a major cause of impairments in visual function, particularly in older women. And in the United States alone, their incidence has been estimated at around 100,000 people [1].

Pathogenesis of Macular Holes

Idiopathic macular holes are distinct from retinal detachment with macular hole, which latter condition is often associated with myopia. In a consecutive series of 80 eyes which had undergone surgery for macular hole, retinal detachment was extant in 66 cases (82.5 %), and among these, myopia and high myopia (>10 diopters) were prevalent (table 1).

Shrinkage of the epimacular vitreous cortex has been recognized as the basic mechanism underlying the pathogenesis of macular holes [2–5]. Neither the development of macular cysts and impending holes nor their progression to full-thickness lesions depend on posterior vitreous detachment [6, 7]; indeed, early-stage macular holes may even regress if the posterior vitreous has detached [7].

Four stages in the clinical development of macular holes may be distinguished [2]: Dehiscence of the foveal receptor layer is defined as im-

Table 1. Prevalence of myopia and proliferative vitreoretinopathy (PVR) in cases of idiopathic macular hole and in those with retinal detachment and macular hole

	Idiopathic macular hole		Macular hole with retinal detachment	
	n	%	n	%
Total number of cases	14		66	
Myopia (≤10 D)	1	7	9	14
High myopia (>10 D)	0	0	31	47*
PVR	5	35[1]	19	29

* $p < 0.001$ (Fisher exact p, two-tailed test).
[1] Epimacular membrane present.

pending macular hole (stage 1). Stage 2 is characterized by the manifestation of small – and stage 3 by that of larger – full-thickness macular holes *without* posterior vitreous detachment, in association with which there is usually a cuff of subfoveal fluid. Stage 4 is attained when complete detachment of the vitreous has occurred. The biomicroscopic manifestation of prefoveal opacification has been suspected of bespeaking a contracted condensation of premacular vitreous cortex [8], and histopathologic analyses of such regions have borne out this impression: these pseudo-opercula are not comprised of retinal tissue [9–11].

Certain cases in which macular pucker or epimacular membrane occur in association with pseudoholes may be falsely diagnosed as true macular holes, but they should be considered as distinct entities [12–15] and not confused with the latter. On the other hand, full-thickness macular holes may, in certain cases, be caused by tangential traction of epiretinal membranes [16], and an association between cystoid macular edema and idiopathic macular holes has been demonstrated histologically [16, 17].

A clinical distinction between pseudo- and full-thickness macular holes may be facilitated by use of a laser aiming-beam test [18], and laser biomicroscopy is known to aid the identification of vitreomacular separation [19]. Optical coherence tomography (OCT) is a new sophisticated technique which permits macular cysts and impending holes to be distinguished from full-thickness ones; it also renders possible a visualization of vitreo-macular separation and measurement of macular hole diameter [20].

Conventional Surgical Methods for the Treatment of Retinal Detachment with Associated Macular Holes

Retinal detachment in association with a macular hole has in the past been treated by posterior scleral indentation either with diathermy, photocoagulation or cryopexy. Posterior scleral indentation was achieved either by use of a radial [21–24] or absorbable fibrin sponge [25], by creating a scleral pocket [26], by subchoroidal implantion of hyaluronic acid [27], or by a silver clip [28–30].

A review of 277 cases, published before 1982, reveals that reattachment was achieved in 74 % of cases [21, 25, 31–34]. According to recent retrospective studies, vitrectomy in conjunction with gas-injection yielded better visual results than did macular diathermy and/or buckling [35, 36]. Aspiration of liquid vitreous followed by intravitreal gas-injection alone, i. e. without effecting scleral buckling and macular coagulation, has been reported to be successful in 16 of 19 cases [37].

Vitrectomy and Fluid-Gas Exchange for Retinal Detachment with Macular Hole

Gonvers and Machemer [38] proposed in 1982 the performance of vitrectomy for the treatment of eyes with retinal detachment and macular holes. The rationale behind a direct vitreoretinal approach was the release of vitreoretinal traction which is recognized as the principal cause of macular holes. Initially, a vitrectomy was combined with coagulation of the macular hole in about 20 % of the cases, hyaluronic acid, gases like sulfur hexafluoride and perfluorpropane, air, or silicone oil [39–42] being used as tamponades. But it subsequently became apparent that this coagulation step was unnecessary, a review of 213 cases published between 1982 and 1986 disclosing the reattachment rate to be as high as 82 % when vitrectomy was performed without macular coagulation [38, 43–54].

Although early macular redetachment after initial surgery may still occur in about 20 % of instances, a final reattachment of the macula is now being achieved in an average of 90 % of cases which have undergone vitrectomy and gas injection [36].

Autologous Blood and Tissue Adhesives for Macular Hole Surgery in Eyes with Retinal Detachment

Early postoperative reopening of macular holes is always a potential threat, especially in highly myopic eyes, and in an endeavor to minimize this risk, various adjunctive measures have been proposed to facilitate macular adhesion.

Since 1985, we began to use autologous blood as a sealant during vitrectomy, particularly in highly myopic eyes which were suspected of having reduced macular adhesion properties owing to posterior chorioretinal atrophy [55]. In a recent retrospective study [unpubl.], we analyzed the postoperative reattachment rate and visual function in 80 consecutive eyes which had undergone vitrectomy for macular holes either in association with or without retinal detachment. Autologous blood was applied to the macular hole after vitrectomy and fluid/air exchange in 40 cases, whilst the other 40 eyes served as controls (no adjunctive treatment with autologous blood). A significant postoperative increase in mean visual acuity occurred only in those eyes which had received topical autologous blood treatment, this being especially so in myopic eyes.

Autologous blood has also been shown to facilitate separation of the posterior vitreous cortex from the macular area [56].

Cyanoacrylate tissue sealants have also proved to be beneficial in improving macular adhesion after vitrectomy. In one study comprised of 9 such cases, 8 of which had previously undergone unsuccessful vitreoretinal surgery, complete reattachment was achieved in 8 instances [57]. And in another series employing such a sealant, visual improvement was reported in 76 % of the instances (n = 15) [58].

Vitrectomy for Impending and Idiopathic Full-Thickness Macular Holes

In recent years, eyes with idiopathic macular holes at stages 2–4 as well as impending ones (stages 1 A and 1 B), have been increasingly considered as candidates for vitreoretinal surgery [59].

Special techniques have been described for the suctioning and peeling away of vitreous cortex, which is often firmly attached to the posterior pole, macular region and optic disc in stage 1–3 macular holes [60, 61]. We have found that the localization and subsequent peeling of adherent vitreous cortex, under indirect ophthalmoscopic control or by use of the operating microscope, may be considerably facilitated by intraoperative automatic air infusion. And intravitreal injection of autologous blood also helps to identify the epimacular vitreous cortex [62].

Conflicting opinions exist on the use of vitreoretinal surgery for impending macular holes. In a randomized multicenter trial, the benefit of vitrectomy for stage 1 macular holes was not borne out: 37 % of operated cases progressed to full-thickness holes compared with 40 % in eyes randomized for observation [63]. But in another study [13], a lower rate of progression occurred in 26 % of the instances. Visual improvement after vitrectomy for stage 1 macular holes has been reported in over 80 % of the cases [12, 61] and appears to be more commonly achieved in such eyes than in those with full-thickness holes.

Albeit so, vitreoretinal surgery is being increasingly undertaken in the latter instances (stages 2–4). Criteria for anatomical success include closure of the hole, i. e. reattachment of the cuff of subretinal fluid, and prevention of subsequent retinal detachment. And on this basis, success is currently being achieved in 58–97 % of the instances [64–73].

Adjunctive Agents Used to Facilitate Healing of Macular Holes

In a series of 23 cases of macular hole with associated retinal detachment, vitrectomy was performed in conjunction with topical application of autologous blood [55]; 57 % of the eyes were highly myopic. Final reattachment of the retina was achieved in 87 % of the instances, and a visual improvement in 78 %. In a larger series of 80 eyes, application of autologous blood to the hole yielded a significantly higher rate of visual improvement than did vitrectomy without such adjunctive treatment (see above; fig. 1).

Human [74] or bovine thrombin, the latter in combination with autologous fibrinogen [75], as well as autologous serum, have been employed as adjuncts both in humans [76–78] and experimental animals [79, 80]. And it has been argued that certain serum cytokines such as those known to act in the capacity of growth factors, could conceivably induce fibrocellular proliferation and thus also facilitate chorioretinal adhesion at the site of a macular hole.

TGF-β2, with its capacity to promote wound healing, appears to be a particularly effective adjunct in macular hole surgery, as evidenced by the high rates of closure and visual improvement achieved [81–85] when it is employed at sufficiently high doses [81]. By use of this agent, it is even possible to avoid peeling of epimacular membranes [83]. And reopened macular holes have also been successfully retreated with TGF-β2 [82, 84, 85]. However, the limited availability and high costs of this substance thwart its general use in macular hole surgery.

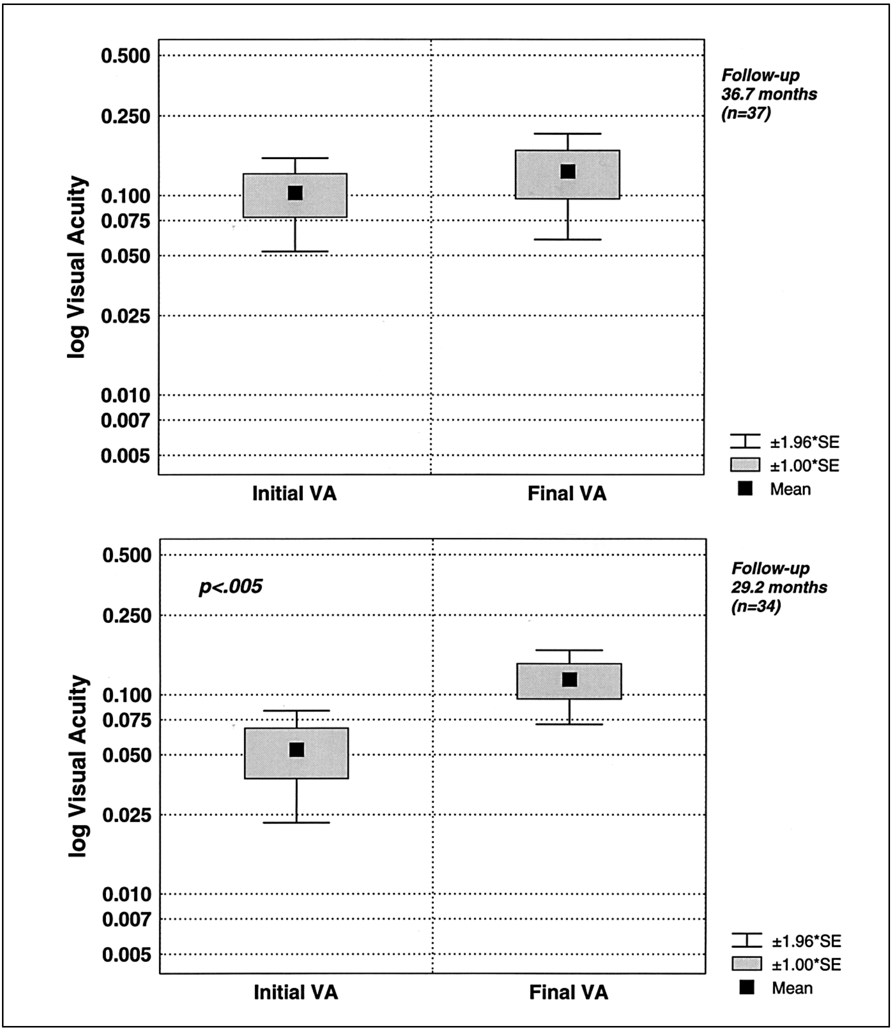

Fig. 1. Initial and final visual acuity (VA) in 37 eyes which had undergone vitrectomy and air- or sulfur hexafluoride-gas injection and in 34 eyes which had additionally received adjunctive application of autologous blood to the macular hole. Five eyes of group 1, and 2 in group 2, had an impending macular hole; all other cases had full-thickness ones. Retinal detachment was present in 73 and 88 % of the instances in groups 1 and 2, respectively. Nine amblyopic eyes were excluded from the total of 80.

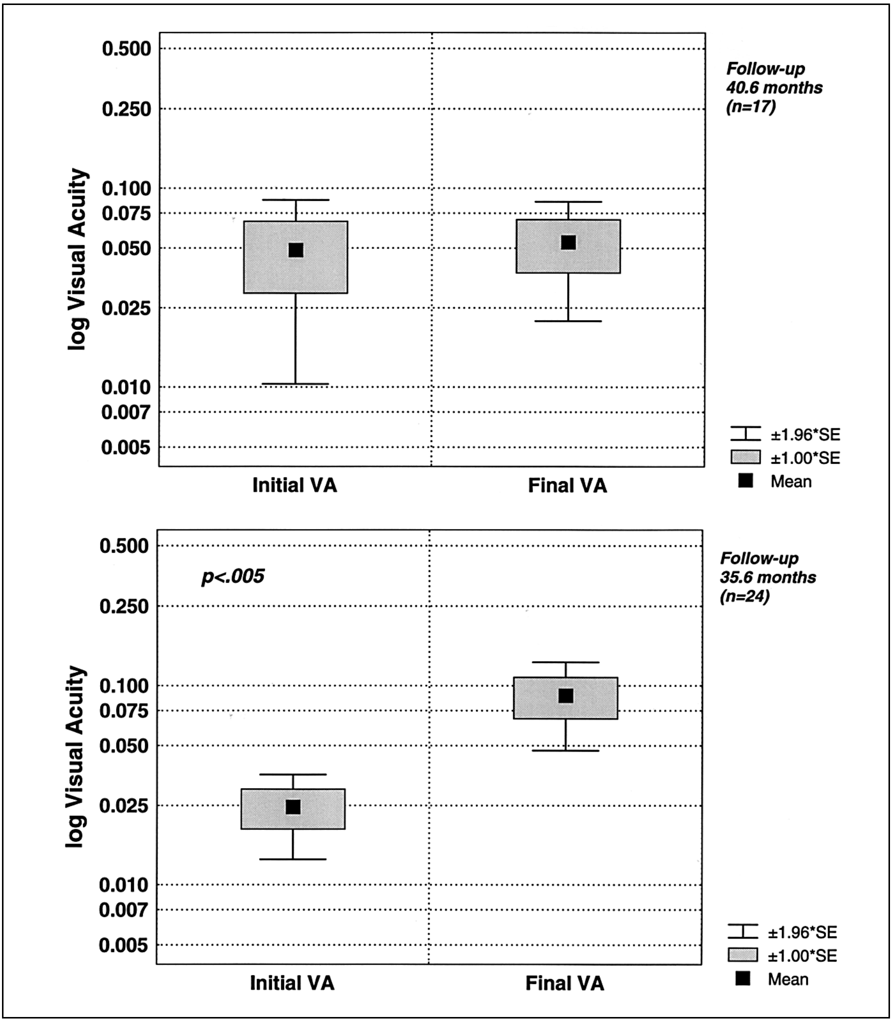

Fig. 2. Initial and final visual acuity (VA) in 17 myopic eyes which had undergone vitrectomy and air- or sulfur hexafluoride-gas injection and in 24 myopic eyes which had additionally received adjunctive application of autologous blood to the macular hole. Retinal detachment was associated with the macular hole in 40 of the 41 eyes.

In two recent studies [71, 73], autologous platelet concentrates were used as adjuncts in the treatment of full-thickness macular holes, flattening of the affected areas being achieved in 95 and 85.7 % of the cases, respectively. In another investigation [71], similar treatment elicited reattachment in 19 of 20 eyes, as against 13 of the 20 which received no such ad-

Table 2. Adjunctive agents currently used to facilitate the healing of macular holes (together with the pertinent literature references)

Adjunctive agent used in vitreoretinal surgery	Reference
Autologous blood	55, 56
Human thrombin	74
Bovine thrombin together with autologous fibrinogen	75
Autologous serum	78–80
TGF-β2	81–85
Platelet concentrate	71, 73

junctive therapy ($p < 0.05$). Preliminary personal observations indicate that comparable anatomical success rates may be achieved by use of either platelet concentrate or autologous blood. The use of autologous serum, blood and platelet concentrates all have the adavantages of easy preparation, and low cost, and their use does not carry the risk of precipitating unwanted immunological reactions (table 2).

Functional Results of Macular Hole Surgery

The visual results currently achieved by macular hole surgery are encouraging, albeit that we are still fairly ignorant of the long-term functional outcome of the untreated condition. Indeed, we are not aware of any prospective study which has been undertaken to compare visual function after vitreoretinal surgery for macular holes with that in a control group of eyes over long observation periods.

Elimination of vitreoretinal traction in stage 1 impending macular holes improves visual function in about 90 % of the cases [12, 13, 61]. And closure of a full-thickness ones also improves visual acuity in most instances [72], superior results being obtained in patients with symptoms of less than 6- to 12-months' duration [66, 69, 70]. Interestingly, bilateral visual function after macular hole surgery in one eye appears to be markedly better in patients with near-normal – than in those with reduced – visual acuity of the fellow eye [86].

Adjunctive application of an appropriate dose of TGF-β2 to idiopathic or traumatic full-thickness macular holes after vitrectomy has been

Table 3. Pre- and postoperative visual acuity in 66 eyes with macular holes and retinal detachment

Visual acuity	PPV with autologous blood		PPV without autologous blood	
	n	%	n	%
Better	23	63.9	9	30.0
Same	7	19.4	14	46.7
Worse	6	16.7	7	23.3
Total number of cases	36		30	

Significantly higher rates of visual improvement were achieved when autologous blood was applied to the macular hole ($p < 0.02$) after pars plana vitrectomy (PPV).

shown to elicit an increase in visual acuity by two lines or more in 40–70 % of the cases [81, 84, 85]. Scanning laser ophthalmoscopic microperimetry of patients with macular hole has revealed absolute scotomata in the region of neurosensory defect as well as relative ones in the zone of perifoveal detachment, and there exists a good correlation between central visual field defects and visual acuity [87]. After vitrectomy with adjunctive TGF-β2, absolute scotomata disappeared and relative ones at least partially resolved [88].

In a personal study of 66 cases, application of autologous blood to the macular holes after vitrectomy for retinal detachment elicited significantly better visual results than did surgery in the absence of such adjunctive treatment (table 3; fig. 1). A similarly favorable functional result was obtained in myopic eyes (fig. 2). Autologous blood contains a variety of growth factors, including TGF-β2, and it seems not unlikely that some of these may play a role in wound healing after vitrectomy, and perhaps incite a regenerative response by the receptor layer and/or retinal pigment epithelium.

Complications

The development of progressive nuclear cataracts is a well-known side effect of vitreoretinal surgery, and their manifestation after macular hole surgery is therefore not surprising; increasing rates of cataract have been reported to occur in up to 76 % of the cases 2 or more years after vitrectomy and instillation of long-acting gases [89].

A specific and so far unexplained complication of macular hole surgery appear to be a visual field defects, particularly in the lower periphery of the field, and in some of these cases an optic-disc pallor may also be observed [90, 91]. Whether these deleterious changes are attributable to surgical manipulation at the epipapillary vitreous cortex, or to the use of long-acting gases, or indeed whether other as yet unknown factors are responsible, remains to be clarified.

Postoperative progression of stage 2 macular holes to the stage 3 or 4 condition has been reported in 20 % of the cases, as against an incidence of 71 % of untreated eyes observed for 12 months or more [92].

The risk of a postoperative increase in intraocular pressure is usually limited to the first two weeks after surgery. If TGF-β2 is employed as an adjunct, then a markedly higher risk (39 %) of increasing intraocular pressure is associated with the recombinant – than with the bovine – form [93].

Postoperative infections or immunological reactions to adjunctive agents have not been reported, although hypopyon-development has been reported in 8 [74] to 28 % [75] of the cases treated topically with bovine thrombin.

Posterior-segment complications have become less frequently in recent years, owing to improvements in vitreoretinal surgical techniques. Formerly, retinal hemorrhaging was commonly observed when using macular buckling procedures [94]. Nowadays, peripheral retinal breaks and/or rhegmatogenous detachment [95] or retinal dialysis [65] are more likely to occur, and these conditions are usually precipitated by remote traction on the vitreous base during aspiration of the nondetached vitreous cortex. Reported rates of late macular hole reopening and recurrent retinal detachment vary between 5 and 15 %, depending on the anatomical situation and surgical technique used [37, 38, 40, 43, 96–98]. Reoperation using an air tamponade, TGF-β2 or silicone oil have proved to be successful in most cases.

Postoperative damage to the retinal pigment epithelium in the macular area [99, 100] is to be expected in eyes with large full-thickness macular holes, retinal detachment and high myopia. And a swelling as well as mottling of this layer may persist after peeling away epimacular membranes and sheets of vitreous cortex [101].

Conclusion

A better insight into the pathogenesis of macular holes has substantially influenced our surgical approach during the past 15 years. It is now known that adherent vitreous cortex and/or epimacular membranes exert centrifugal traction on the inner perifoveal layers. But the cause of the adhesive forces which prevent posterior vitreous detachment in these patients remains to be elucidated.

Initial symptoms of the vitreomacular traction syndrome include loss of visual acuity and metamorphopsia, and their early recognition permits surgical removal of vitreous cortex and epimacular membranes before the development of a full-thickness macular hole. The functional results of vitrectomy for impending macular holes are particularly good.

Closure of full-thickness macular holes is achieved by vitrectomy and air or gas tamponade in a substantial number of cases. And the adjunctive application of autologous blood, serum, transforming growth factor or a platelet concentrate to the macular hole yields a surprisingly high rate of visual improvement. The same holds true for similarly treated cases of retinal detachment with associated macular holes, although the final visual acuity remains at lower levels, owing to morphological changes in the macular region, in these frequently myopic and sometimes amblyopic eyes.

In general, anatomic and functional success rates justify the application of vitreoretinal surgery in conjunction with agents known to facilitate chorioretinal wound healing at the site of a macular hole.

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