

EXTENDED REPORT

A randomised controlled feasibility trial of vitrectomy versus laser for diabetic macular oedema

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Aim: (1) To evaluate whether vitrectomy is preferable to further macular laser in improving visual acuity and resolving retinal thickening in patients with diabetic macular oedema (DMO) despite previous laser and no macular traction. (2) To determine the feasibility of further trials in this population in terms of magnitude of comparative clinical effect, rate of recruitment, and loss to follow up.

Methods: A randomised controlled feasibility study. Patients with DMO and a visual acuity of 0.3 logMAR (6/12) or worse after one or more macular laser treatments were randomised on a 1:1 basis to either pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling or further macular laser. Patients with a posterior vitreous detachment, biomicroscopic evidence of retinal traction, or a taut thickened posterior hyaloid (TTPH) were excluded. Primary outcome measures were (1) best corrected logMAR visual acuity, (2) mean central macular thickness on optical coherence tomography, and (3) rate of recruitment and loss to follow up. Analysis was on an intention to treat basis.

Results: 19 patients were randomised to PPV and 21 to further macular laser. The mean baseline logMAR visual acuity was 0.65 (SD 0.28) for the group randomised to PPV and 0.60 (0.23) for the group randomised to laser. The mean change in best corrected visual acuity of the vitrectomy group was deterioration by 0.05 logMAR, while in the control group the mean change was an improvement of 0.03 logMAR. The median (interquartile range) baseline central macular thickness was 403 (337, 492) for the group randomised to PPV and 387 (298, 491) for the controls randomised to laser. The median change in central macular thickness from baseline to review in the vitrectomy group was a thinning by 73 μ m (20%) and by 29 μ m (10.7%) in the control laser group. This single centre was able to recruit 40 patients in 18 months with follow up of 82% at 1 year.

Conclusion: A randomised controlled trial was found to be potentially feasible in this population, the rate of recruitment was however slow and one in five patients were lost to follow up because of death and ill health. These data provide little evidence in terms of visual acuity and macular thickness of any benefit of vitrectomy over further macular laser in patients with an attached hyaloid, DMO despite previous laser, and no clinically evident macular traction or TTPH.

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Laser has a proved role in the management of diabetic macular oedema (DMO).^{1,2} It might however be expected to fail to control the oedema in one third of patients and, while preserving fixation, results in pericentral field loss.³ There are reports suggesting that pars plana vitrectomy (PPV) might be an effective and/or preferable treatment for DMO.^{4–18} The available data are however predominantly uncontrolled and retrospective with non-standardised follow up. They also include patients from potentially important and differing prognostic groups such as those with a taut thickened posterior hyaloid (TTPH),^{4–7} macular traction, and the presence or absence of a posterior vitreous detachment.^{9,15,16}

With the aim of defining the feasibility and size of a subsequent randomised trial we have therefore performed a randomised controlled feasibility study which aimed to:

- (1) provide unique controlled data regarding the comparative efficacy of vitrectomy and further macular laser in patients with DMO despite previous laser treatment, an attached hyaloid and no clinical evidence of either macular traction or a TTPH;
- (2) provide data on rate of recruitment, loss to follow up, and clinical outcome with which to inform the sample size and power of future trials in this population.

METHODS

This is a single centre randomised controlled trial. Potentially eligible patients were recruited from the clinics of local

collaborating medical retina specialists. Ethical approval was obtained before commencing this study from the Guy's and St Thomas' research ethics committee (EC00/004). A study size of 40–50 patients randomised into two equal sized blocks was selected.

The following inclusion criteria were applied: (1) a confirmed diagnosis of diabetes mellitus, (2) clinical and angiographic evidence of diffuse or focal macular oedema in an eye which had already received at least one argon laser treatment not less than 3 months previously,^{1,19} (3) a visual acuity of 0.30 logMAR (Snellen equivalent 6/12 or 20/40) or worse, (4) able and willing to give informed consent and participate in the trial assessment protocol.

Patients were excluded on the basis of the following: (1) co-existing eye disease liable to affect visual outcome, (including axial or capsular lens opacity, glaucoma, amblyopia and non-diabetic macular disease), (2) ischaemic maculopathy as defined by Bresnick *et al*,²⁰ (3) active proliferative diabetic retinopathy, (4) vitreous haemorrhage, (5) biomicroscopic evidence of macular traction including epiretinal membrane, vitreoretinal traction arising from proliferative retinopathy, and a TTPH (that is a thickened, taut, and glistening premacular posterior hyaloid without evidence of retinal striae⁴), (6) a clinically evident posterior vitreous

Abbreviations: DMO, diabetic macular oedema; ICG, indocyanine green; ILM, internal limiting membrane; IQR, interquartile range; OCT, optical coherence tomography; PPV, pars plana vitrectomy; TTPH, taut thickened posterior hyaloid

detachment defined as the presence of a Weiss ring or a continuous folded layer of optically dense vitreous behind which no normal vitreous structures could be visualised, (7) uncontrolled hypertension (BP >140/95 mm Hg), and (8) severe renal impairment as determined by the need to undergo renal replacement therapy.

Patients were assessed at the baseline and follow up visits in accordance with a standardised protocol. Best corrected logMAR visual acuity measurements were obtained by one of two optometrists trained in protocol ETDRS refraction under standardised conditions using the method of full interpolation.²¹

Optical coherence tomography (OCT, Zeiss, Dublin, CA, USA) central macular thickness measurements were obtained using optimised polarisation and a 5.92 mm six radial line scan protocol (OCT 2) centred on the fovea via an internal fixation beam. The measurement employed was the mean of the six measurements of thickness at fixation calculated using the inbuilt macular thickness algorithm (Humphrey Zeiss Version 6.2). Biomicroscopic examination of the macula was performed using a Volk super-66 and/or Goldmann fundus contact lens. Fundus fluorescein angiography was performed by a trained photographer using the standard 30 degree seven field Diabetic Retinopathy Study protocol.¹⁹ Scheimpflug lens photography with measurement of both central nuclear density and retroillumination area was performed by one trained observer using the Nidek EAS-1000 system. In addition to these tests the patient underwent measurement of blood pressure, glycosylated haemoglobin, and serum creatinine.

Case notes were reviewed to determine the extent and type of previous laser treatments. Using the system employed by Pendergast *et al*,⁶ previous treatment was categorised into light, moderate, or heavy macular laser and panretinal photocoagulation.

Patients who met the eligibility criteria and agreed to participate in the study were randomised to undergo the intervention of vitrectomy or the control treatment of further laser within 1 month. Treatment allocation for each patient was determined by the opening of a sealed, numbered, opaque envelope. The randomisation sequence was on a 1:1 basis in blocks of an unknown and variable size. The randomisation sequence was prepared by a medical statistician not involved in the conduct or analysis of the trial and the envelopes were opened by one of the clinical investigators (DT).

The intervention group underwent standard three port pars plana vitrectomy with induction of a posterior vitreous detachment followed by 0.5 mg/ml indocyanine green (ICG) assisted internal limiting membrane peeling. All surgery was performed by a single surgeon (DAHL). The control group underwent further argon laser macular grid treatment to areas of angiographically confirmed leakage by one surgeon (DT) using the ETDRS protocol.²² In cases where both eyes met the entry criteria the study eye was selected as the one with the acuity nearest to 0.60 logMAR (6/24 or 20/80 Snellen, 0.25 decimal Snellen). The fellow eye received standard care.

For trial purposes patients were reassessed at 12 months post-randomisation; they also attended for routine clinical review at 3, 6, and 9 months after treatment. Patients in either arm who demonstrated treatment failure (defined as unchanged or worsened macular oedema and visual acuity at 6 months following trial treatment) were offered further argon laser photocoagulation.

Outcome measures were identified a priori. The following primary outcome measures were employed: (1) best corrected ETDRS logMAR visual acuity, (2) central macular thickness on OCT, and (3) the rate of recruitment and loss to follow up in this patient population.

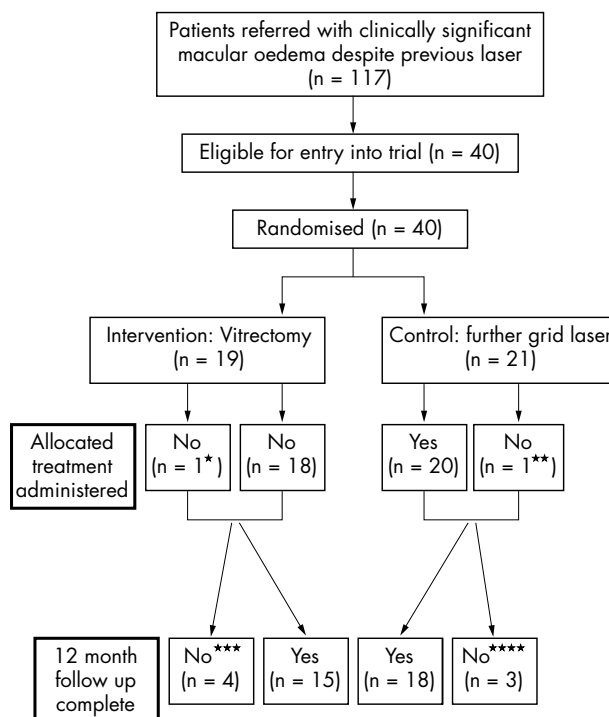


Figure 1 A flow diagram of patient recruitment and follow up. *Patient developed cardiovascular problems and was unfit for surgery. **Patient resolved completely before treatment. ***Patients died before completing the trial protocol. ****One patient died before completing the trial protocol and two patients were unable to attend because of debilitating illness.

The secondary outcome measures were: (1) complication rates, (2) rate of treatment failure, (3) proportion of patients improving by three or more lines of logMAR visual acuity, (4) proportion of patients showing a 30% or greater reduction in central macular thickness, and (5) progression of lens opacities.

Baseline characteristics of patients in each treatment group were summarised. Data were analysed according to the group to which patients were originally allocated (that is, intention to treat). Summary statistics for visual acuity and central macular thickness in each treatment group were computed. An analysis of covariance was conducted to assess evidence of a treatment effect with regard to visual acuity and central macular thickness. This was repeated with adjustments being made for imbalances in prognostic factors evident at baseline and for cataract progression for the visual acuity analysis. Secondary outcomes were tabulated by treatment group.

RESULTS

Recruitment and follow up are presented in figure 1. In all, 117 patients were referred over a period of 18 months for consideration of inclusion in this trial. The study patients were derived from collaborating eye clinics which serve a total population of 2.3 million patients; 77 patients (68%) did not satisfy the trial inclusion criteria. Reasons for this included a posterior vitreous detachment (14 patients, 12%), a TTPH (six patients, 5%), and clinically evident macular traction (six patients, 5%). Other reasons were active proliferative retinopathy, ocular co-morbidity, visual acuity better than 0.3 logMAR, no persistent DMO, uncontrolled hypertension, renal failure, and either unable or unwilling to undergo randomisation and follow up in accordance with the trial protocol.

Forty patients were considered eligible for randomisation and all 40 agreed to participate in the trial. Twenty one were

Table 1 A baseline comparison between the intervention and control groups

Baseline comparison between the intervention and control groups		Control group (further laser) (n=21)	Intervention group (vitrectomy) (n=19)
		No (% or SD)	No (% or SD)
Age (years)		64.2 (9.98)	64.3 (10.69)
Sex	Female	6 (29%)	8 (42%)
	Male	15 (71%)	11 (58%)
Ethnicity	Afro-Caribbean	1 (5%)	0 (0%)
	White	19 (90%)	18 (95%)
	Indian	1 (5%)	1 (5%)
Type of diabetes	Type 1	2 (10%)	1 (5%)
	Type 2	19 (90%)	18 (95%)
Insulin controlled	Yes	11 (52%)	15 (79%)
Blood pressure (mm Hg)	Systolic	140 (16)	136 (14)
	Diastolic	77 (11)	77 (9)
HbA _{1c} %		7.7 (1.4)	8.8 (1.5)
Serum creatinine (mmol/l)		108.5 (41.6)	103.2 (32.5)
Median duration of diabetes (years) [IQR*]		11 ^{8 16}	14.5 ^{10 20}
Past history of laser treatment	Heavy macular laser (>300 burns)	14	12
	Moderate macular laser (126–300 burns)	5	4
	Light macular laser (<126 burns)	2	3
	Panretinal photocoagulation	3	4
ETDRS logMAR visual acuity mean (SD)		0.60 (0.23)	0.65 (0.28)
OCT central macular thickness (µm) median [IQR]		403 [337, 492]	387 [298, 491]
Median central nuclear density (%) [IQR]		33.05 [30.0, 42.5]	33.85 [29.6, 49.0]

*IQR, interquartile range.

randomised to undergo further laser (control group) and 19 to the intervention of vitrectomy. Table 1 presents a comparison at baseline of the control and intervention groups.

Two patients did not undergo the allocated treatment. One patient allocated to the laser (control) group developed spontaneous resolution of macular oedema with a corresponding improvement in his visual acuity. Laser treatment was therefore withheld but follow up occurred in accordance with the trial protocol. One patient allocated to the vitrectomy group died before surgery.

In the control (laser) group the median time between randomisation and treatment was 27 days with a range of 7–49 days. In the vitrectomy group the median time between randomisation and treatment was 53 days with a range of 12–176 days. Patients who had a latency of more than 60 days between randomisation and treatment underwent immediate pretreatment repeat baseline acuity and central macular thickness measurements and we found no evidence of any significant change in either measure.

One year follow up was completed in 33/40 patients (82%). This consisted of 14/19 (74%) patients in the vitrectomy group and 19/21 (90%) of those randomised to laser. Of the defaulters five had died and two were too ill to attend.

The trial primary and secondary outcome measures are presented in tables 2, 3, and 4.

DISCUSSION

At the time of writing there are 537 cases reported in the literature of patients who have undergone vitrectomy as a treatment for diabetic macular oedema.^{4–18} In 114 cases the patients displayed the clinical constellation of a TTPH.^{4–7 12 13} In 28 cases the patients were reported to have macular traction in the form of an epiretinal membrane^{15 16} and in a further 43 cases a posterior vitreous detachment was present.^{9 15 16} In the remaining 307 cases the patient presented with DMO that had not responded to laser and in whom neither traction, a TTPH nor a posterior vitreous detachment was present.^{8 10 11 13–18 23–28} Of 117 patients considered for inclusion in this trial, only 26 (22%) were excluded on the basis of a PVD (12%), TTPH (5%), or macular traction (5%). Using this vitreomacular interface based classification it appears that the group which we have selected for study is the one most frequently encountered in clinical practice.

Several authors have published data suggesting that vitrectomy improves visual acuity and/or reduces macular thickness in this group of patients with an attached hyaloid and no signs suggestive of macular traction.^{8 10 11 14–17 23–28} Only one study of eight patients has suggested that the procedure may not be effective in this context and this study reported initial resolution with rapid recurrence.¹³ Despite the number of cases and reports only two studies have been

Table 2 The primary outcome measures of the trial

	Control group n=18 (further laser)			Intervention group n=15 (vitrectomy)		
	12 months	Change	% Change	12 months	Change	% Change
ETDRS logMAR visual acuity mean (SD)	0.57 (0.33)	-0.03 (0.25)	-2.93 (44.33)	0.72 (0.33)	0.05 (0.26)	17.37 (52.44)
OCT central macular thickness (µm) median [IQR*]	338.5 [257, 459]	-29 [-162, 77]	-10.7 [-42.6, 42.5]	272 [214, 394]	-73 [-183, 27]	-20 [-45.4, 8.0]

*IQR, interquartile range.

Table 3 The results of analysis of covariance to investigate the statistical significance of the trial primary outcome measures

	Model 1		Model 2	
	Coefficient	p Value	Coefficient	p Value
ETDRS logMAR VA	0.099	0.277	0.265	0.123
OCT central macular thickness	-20.178	0.746	-7.289	0.919

Model 1: adjusted for baseline differences in acuity and central macular thickness only.

Model 2: adjusted for baseline differences in acuity, central macular thickness, insulin use, duration of diabetes, and glycosylated haemoglobin. Model 2 for ETDRS logMAR visual acuity was additionally adjusted for cataract progression.

controlled and neither was randomised; one series employed fellow eyes and the other was a retrospective case control series.^{11 28}

A randomised trial of this question was required. There were, however, insufficient data on the likely rate of recruitment, loss to follow up, and comparative magnitude of the clinical effects upon which to base a sample size estimate. To expand on this point, all data of which we are aware pertaining to the outcome of laser for DMO do so in the context of new cases rather than those in whom oedema persists despite treatment.^{1 2} There are no prospective data determining the change in central macular thickness or visual acuity at 1 year in patients with DMO undergoing vitrectomy; and the willingness of such patients to be referred to a regional centre, undergo randomisation to primary vitrectomy, or laser (as opposed to standard further focal or grid laser) and attend for follow up has not been tested. A trial with 90% power to detect at the 5% significance level a difference of 0.20 logMAR at 1 year between an intervention and control group such as ours at baseline would require complete follow up of 58 patients per group which with our approximately 20% rate of loss to follow up would have necessitated the recruitment of 140 patients. Ethical and funding considerations mean that it is important to be able to demonstrate that a trial of this size is potentially feasible rather than based on speculative assumption. We have therefore performed a randomised study of a deliberately limited size from which to determine the need, feasibility, and sample size of a subsequent larger trial.^{29 30} The sample size of 40–50 patients was arbitrarily arrived at on the basis of being potentially achievable within 12–18 months of onset, the slightly uneven size of the groups is explained by the fact that 40 as opposed to 50 patients were recruited.

One hundred and seventeen patients were referred over the course of 18 months for consideration of inclusion in the trial, 40 of whom were found to be eligible and agreed to participate; 33 out of 40 (82.5%) of these patients were followed up to 12 months. Of the seven patients lost to follow up five had died and the other two were too ill to re-attend.

The rate of referral to a regionally based trial obviously reflects the prevalence of disease in the community and vigour of the referring clinicians in initiating recruitment. The collaborating ophthalmologists who referred patients to this trial are estimated to serve a population of 2.3 million. Extrapolation from this to other populations or trials may be of questionable significance; we were however able to recruit at a rate of 11 patients per million of the population per year. From these results we conclude that further trials of this nature, while feasible, are likely to suffer from slow recruitment and/or require a very large “catchment” population. A high rate (approximately 20%) of unavoidable loss to follow up might also be anticipated.

The chronic nature of DMO, latency from laser treatment to response and reports of oedema recurrence following vitrectomy all suggested that at least 1 year follow up would be required in the trial design. A 0.3 logMAR change in acuity was selected as this represents the definition of moderate visual loss as employed in the ETDRS studies.^{1 31}

The baseline demographic and medical characteristics of patients entered into the trial are shown in table 1. Our study group was typical of previously reported populations with an average age of 64 years, predominantly type 2 diabetes and a mean acuity at baseline of 0.62 logMAR (Snellen equivalent 6/25 or 20/83). They were also very similar to previous reports in terms of duration of diabetes, blood pressure, glycosylated haemoglobin, renal function and previous macular laser.^{8 10 11 13–17 23 25 32 33} One major difference between our trial population group and those patients included in previous reports is ethnic mix: 15 of the 20 reports on the efficacy of vitrectomy for DMO in the absence of a posterior vitreous detachment, TTPH or macular traction have derived from Japan^{8 10 11 13–18 23–28}; 37 out of 40 patients in this trial were white.

With three exceptions the randomisation sequence resulted in balanced groups (table 1). The exceptions were duration of diabetes, 14 years in the intervention group versus 11 years in the controls, glycosylated haemoglobin (respectively 8.8% and 7.7%), and insulin use (respectively 79% and 52%). These

Table 4 The secondary outcome measures of the trial

Secondary clinical outcome measures at 1 year	Further laser (control group) (n = 18)	PPV (intervention group) (n = 15)
Number (%) patients improving by 0.3 logMAR compared with baseline	2 (11%)	1 (6%)
Number (%) patients with a 30% or greater reduction in OCT central macular thickness	6 (33%)	7 (47%)
Number of patients demonstrating treatment failure 6 months after intervention	8	5
Median central nuclear density [IQR*]	35.48 [30.35, 38.45]	45.01 [31.85, 58.65]
No (%) of patients developing complications	0	1

*IQR, interquartile range.

factors were taken into account via analysis of covariance. In other respects the control and intervention groups appeared similar (table 1).

Another significantly biasing or confounding factor may have been the latency between randomisation and treatment. In the laser group the median time between randomisation and treatment was 27 days with a range of 7–49 days. In the vitrectomy group the median time between randomisation and treatment was 53 days with a range of 12–176 days. Follow up schedules were, however, based on the time following treatment as opposed to the time following randomisation. Patients who had a latency of more than 60 days between randomisation and treatment underwent immediate pretreatment repeat baseline acuity and central macular thickness measurements and we found no evidence of any significant change in either measure. We do not believe that this difference has significantly biased the results.

It may be seen from tables 2–4 that the results of this trial do not support the hypothesis that vitrectomy is preferable to further macular laser in patients with DMO despite previous laser treatment, an attached vitreous, and no clinical evidence of either macular traction or TTPH. The mean change in best corrected visual acuity of the vitrectomy group was deterioration by 0.05 logMAR (or half a line on an ETDRS logMAR chart). In the control group a marginal mean improvement of 0.03 logMAR or a third of a logMAR line was observed (table 2). Only 6% (1/15) of those in the vitrectomy group compared with 11% (2/18) of those in the lasered controls improved their acuity by 0.30 logMAR (table 4). The median change in central macular thickness from baseline to review in the vitrectomy group was a thinning by 73 µm or 20% of the baseline value. In the control group the corresponding figures were a thinning of 29 µm or 11% of the baseline value (table 2). The proportion of patients in each group who reduced their macular thickness by 30% was similar at 39% and 47% respectively (table 4). We do not consider any of these acuity or OCT differences to be clinically significant. In addition to this, no statistically significant differences were found between the groups in terms of these results, either on univariate analysis or ANCOVA taking into account baseline differences in acuity, thickness, duration of diabetes, glycosylated haemoglobin, and insulin use (table 3). The effect of progression of lens opacity between baseline and review on visual outcome was also assessed using analysis of covariance (table 3). It should be noted that the baseline and review central nuclear density values in each group (tables 1 and 4) were compatible with grade 1 nuclear opalescence out of five using the Oxford Clinical Cataract Grading System^{34 35} (CJ Hammond, personal communication, 2003). The observed post-vitrectomy nuclear change within 1 year of surgery did not appear to be clinically significant and is in stark contrast to the marked development of secondary nuclear sclerotic cataract which occurs after vitrectomy in similarly aged non-diabetic eyes.^{36–38} One caveat in the interpretation of these data is that they specifically apply to patients with DMO despite previous laser treatment, an attached vitreous, and no clinical evidence of either macular traction or a TTPH. We do not know whether vitrectomy may be preferable in patients presenting de novo with untreated macular oedema.

Peeling of the internal limiting membrane (ILM) was performed in the vitrectomy group in an attempt to ensure that any subclinical tractional elements or retinal surface diffusion barrier which may have been present was removed.¹² ILM peeling is greatly facilitated by ICG staining. Since the inception of this trial concerns have been expressed about potential retinal toxicity resulting from ICG assisted ILM peeling.^{39 40} The concentration employed was 0.5 mg per

ml and the contact time was as short as possible. We are not aware of any case series in which toxicity has been suggested with this dose and minimum contact time. Where ICG toxicity has been implicated, pigmentary change has been identified and cystoid macular oedema has not been an issue.^{39–43} We did not observe any patients with worsened vision despite resolution of oedema.

These trial data are at odds with all but one of the previous publications regarding the effectiveness of vitrectomy in this group of patients.^{8 10 11 13–18 24–28} At the time of writing we are not aware of any other published data derived on this subject from a randomised controlled trial. Our study design therefore overcame problems of retrospective review, non-systematic follow up and both selection and reporting bias. The trial population was however relatively small at only 40 patients and ethnically different from the majority of previously reported cases.

The results of this randomised control trial do not support the hypothesis that vitrectomy is preferable to further laser in patients with DMO, an attached posterior hyaloid, and no macular traction. There is insufficient evidence from this randomised controlled feasibility trial to justify proceeding to larger trials of this question in this specific group.

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