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Research Article

Survival Rates of Patients Undergoing Vitrectomy for Proliferative Diabetic Retinopathy

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Maria T Sandinha[1,2], George Morphis[1], Deborah M Broadbent[1], Simon P Harding[1], Balasubramanian Ramasamy[1], Ian Pearce[1], Caspar Geenen[2]*, David Wong[1,3], Ian McKay[4] and Heinrich Heimann[1]
[1]Royal Liverpool University Hospital, Liverpool, UK
[2]Sunderland Eye Infirmary, Sunderland, UK
[3]Eye Institute, HBHA Centre, LKS University of Hong Kong, Hong Kong
[4]Sherbrook Consultants, Glasgow

Abstract

Purpose: To describe survival rates of patients with diabetes undergoing vitrectomy and relate these to clinical risk factors.

Methods: Patients undergoing their first vitrectomy for proliferative diabetic retinopathy in a UK regional surgical retina service in 2000 and 2006 were identified (group A). A second group was identified from those undergoing screening for diabetic retinopathy (group B) in 1998. Survival (determined up to July 2011) and risk factors (hypertension, hypercholesterolemia, nephropathy, and neuropathy) were analysed by the Kaplan-Meier life method.

Results: The 3 and 5 year survival rates for group A were 69% (60/87) and 49% (43/87) and for group B 91% (132/145) and 83% (120/145), respectively. All cases in group A with known cardiac disease had died within 5 years of their surgical procedure. The difference between group A (n=87) and group B (n=148) for overall survival was highly statistically significant ($p < 0.0001$).

Conclusions: Vitrectomy in patients with diabetes is a predictor of reduced life expectancy, particularly in the presence of cardiovascular disease. Our work highlights the urgent need to improve the quality of medical care in patients with 'high risk' eye disease. This should be focused on by diabetologists and ophthalmologists and specific care pathways developed for these patients.

Keywords: Diabetes, Retinopathy, Complications, Survival, Mortality, Vitrectomy

Introduction

Diabetes mellitus (DM) is a major medical problem throughout the world. In 2013, there were an estimated 3.0 million (6.6%) people between 16 and 79 years old with diabetes in the United Kingdom (UK), and this number is projected to rise to 3.6 million (7.4%) by 2035 [1]. Diabetes remains associated with an excess risk of mortality in all age groups over 20 in the UK [2]. Proliferative diabetic retinopathy (PDR), one of the main microvascular complications of DM, has a major impact on the quality of life. Laser photocoagulation remains the standard treatment, with vitrectomy being an established treatment for complications of PDR [3]. The main indications for surgery are non-clearing vitreous haemorrhage (VH) and tractional retinal detachment (threatening or involving the macula). To our knowledge there is only one previously published epidemiological study on survival rates after vitrectomy in patients with diabetes in the UK population [4]. The other few published epidemiological studies on survival of diabetic patients after vitrectomy have related to different populations [5-9].

We investigated the survival of patients with PDR undergoing vitrectomy in a UK regional surgical retina service and the relationship with systemic risk factors. In addition, we described a predictive relationship between vitrectomy and death using a population from our well established and comprehensive diabetic screening programme.

Methods

All patients undergoing their first vitreoretinal operation for PDR in calendar years 2000 and 2006 (Group A) were identified from the operating theatre database. These years were chosen to give a minimum of 10 and 5 years follow up, respectively, in order to compile meaningful mortality statistics. Data on age, gender, age at

***Corresponding author:** Caspar Geenen, Sunderland Eye Infirmary, Sunderland, UK,
Email: caspargeenen@gmail.com

diagnosis, duration of DM, insulin usage and survival status were obtained from cases notes. Presence of coronary heart disease (CHD) (history of myocardial infarction, angina, cardiac medications or electrocardiographic evidence of ischaemia), hypertension (systolic >140mmHg), high cholesterol levels (>5mmol/lt, >200mg/dl), nephropathy (patient aware of kidney disease, undergoing dialysis, undergone renal transplantation), neuropathy (reported sensory abnormality) and number of vitreoretinal operations were also recorded. This study adhered to the tenets of the Declaration of Helsinki. Consent for the use of data for research and audit was routinely obtained prospectively from patients. Institutional board approval was not required because this was a service evaluation.

Type 1 DM was defined as age of onset <30 years with insulin usage and Type 2 as onset ≥40 years of age. Patients with onset between 30 and 39 years were classified as Type 1 if they were on oral hypoglycaemic agents for less than 1 year before insulin initiation, and Type 2 if they were on tablets for more than 1 year prior to insulin.

For comparison, survival status in a random sample of patients undergoing screening for diabetic retinopathy in a systematic programme between 05.01.98 and 22.12.98 (Group B) was examined. This time period was chosen to give adequate follow up to assess survival status in this group. The screening programme in Liverpool is comprehensive with high coverage and has been in place for over 20 years. Survival status was determined up to July 2011. Patients dying from a disease not related to diabetes and other risk factors were excluded from the cohort. Data from Group B was used to demonstrate the difference in survival rates in patients without sight threatening diabetic retinopathy. The groups were not matched.

Data were analysed by the Kaplan-Meier procedure. For univariate analysis of risk factors, cumulative survival was compared using the log rank test and the Wilcoxon method: a result was considered of statistical significance if it was significant with both tests. For multivariate risk factor analysis we used the Regression with Life Data facility of Minitab 13.1, which applies a Newton-Raphson algorithm to derive a maximum-likelihood estimate of the model parameters, and tests their significance by a z-test.

Results

Two hundred and thirty two patients were included, comprising 87 vitrectomy patients (Group A) and 145 other diabetic cases (Group B). The clinical and demographic data for the two groups of patients are shown in Table 1. The groups differed with regard to duration of diabetes, estimated mean age of onset and proportion on insulin.

In Group A, seventy five operations were carried out for VH and 22 for tractional retinal detachment; 10 patients were operated on twice. One patient with florid diabetic retinopathy received a pre-operative injection of bevacizumab. The mean age at onset of DM was 37 years (range 4 to 70). Thirty three patients in group A (38%) were classified as Type 1 and 54/87 (62%) as Type 2, of whom 14 were using insulin. Thirty three patients died during the follow-up period; the mean time of survival after first operation was 2.5 years (range 12 days - 7.5 years) and the mean age at death was 68 years (range 24-92 years). Mean time between surgery and last follow-up for survivors was 3.8 years (range 3 months - 9.9 years). Systemic events identified at first operation were distributed as follows: history of heart disease 36/87 (41.4%), high cholesterol 49/87 (56.3%), hypertension 73/87 (83.9%), nephropathy 20/87 (23%) with 8/87 (9.2%) on dialysis and neuropathy 17/87 (19.5%). Missing data comprised: age at onset of diabetes 16/87 (18.3%), cholesterol 7/87 (8%) and renal status 2/87 (2.2%).

Patient characteristics	Patients undergoing vitrectomy (group A)	Non-vitrectomy patients (group B)
N	87	145
Male	47	72
Female	40	73
Mean age at onset of diabetes (years)	37	57
Mean duration (years)	24	5.5
Mean age at start of study (years)	58	62
Patients on insulin	47/87 (54%)	11/145 (8%)
Mean age at death (years)	68	75

Table 1: Clinical and Demographic Characteristics for Groups A and B.

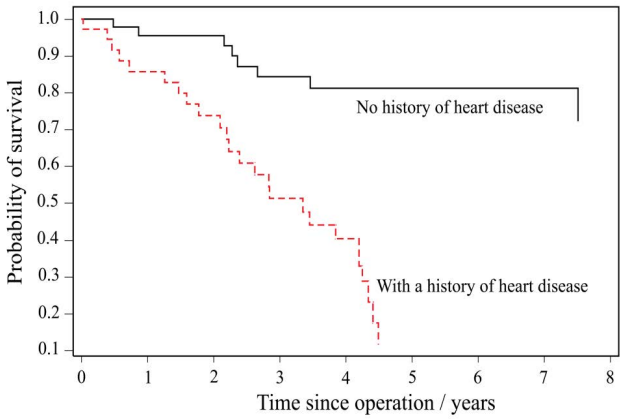

Figure 1: Survival of patients with and without a history of heart disease in the vitrectomy group (Group A). Nonparametric survival plot using the Kaplan-Meier method.

Group B consisted of a random computer selection of the 4601 patients screened in 1998. In 3 patients there was no information about their survival status and these patients were excluded, leaving a total of 145 patients for analysis. The mean age at onset of DM was 57 years (range 19-88) with a mean duration of 5.5 years (range 2 months - 28 years). Nine patients were classified as Type 1 and 134 as Type 2, of whom 2 were using insulin.

In group A on univariate analysis the following factors were significantly associated with poorer survival after vitrectomy: evidence of CHD (log rank and Wilcoxon both $p<0.001$) and neuropathy (log rank $p=0.003$, Wilcoxon $p=0.027$). The relationship between survival and heart disease in Group A is illustrated in Figure 1. The 3 year survival rates of patients with CHD or neuropathy were 0.51 ± 0.09 and 0.50 ± 0.13 respectively. No association with age, sex, duration of disease or type of treatment was detected. Results of a multivariate analysis that included age, CHD, nephropathy, neuropathy and type of diabetes indicated that CHD was the most important risk factor

for survival. The 3 and 5 year and median overall survival rates of Group A are shown in Table 2: the median survival for all patients undergoing vitrectomy was 4.5 years. All patients with either CHD or neuropathy had died in less than 5 years following their first surgical procedure. Patients without these risk factors had greater survival rates so that their median survival times could not be calculated because they were never reached.

Table 3 shows the mortality differences between the two groups, in the form of probability of surviving. The 3 year death rate of group A was 3.4 times higher than of group B [(1-0.69)/(1-0.91)]. The 5 year death rates differed by a factor of 3 [(1-0.49)/(1-0.83)]. For vitrectomy patients with a history of CHD, the death rate over a 3 year or 5 year period was more than 5 times that of patients with diabetes in general. The greater mortality of those patients requiring vitrectomy, compared to those patients not requiring surgery, is shown in Figure 2. The difference between these two groups for overall survival was statistically highly significant ($p < 0.0001$) by both the log-rank method and the Wilcoxon method.

Discussion

In this study we aimed to describe a predictive relationship, not a causal one, between vitrectomy and survival. For this purpose, confounding factors did not need to be eliminated or controlled for. We demonstrated that vitrectomy in patients with DM is a predictor of reduced life expectancy, particularly in the presence of cardiovascular disease. The 3 and 5 year death rates for diabetic patients requiring vitrectomy were 3.4 and 3 times that for patients not undergoing vitrectomy. Coronary heart disease was a major risk factor associated with a significantly elevated death rate. Neuropathy was also associated with shorter survival rates, but this association was weaker and statistically less significant.

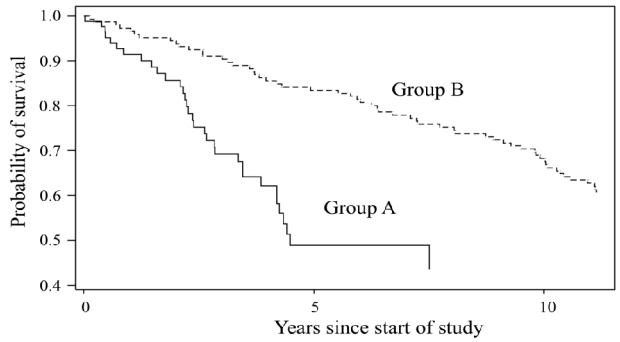

Figure 2: Survival of patients in the vitrectomy group (Group A) and the non-vitrectomy group (Group B). Nonparametric survival plot using the Kaplan-Meier method.

Subgroup	Proportion surviving 3 years	Proportion surviving 5 years	Median survival (years)
All patients undergoing vitrectomy	0.69 ± 0.06	0.49 ± 0.07	4.5
History of heart disease	0.51 ± 0.09	0	3.4
No history of heart disease	0.84 ± 0.06	0.81 ± 0.06	Not calculable
History of neuropathy	0.50 ± 0.13	0	4.2
No history of neuropathy	0.75 ± 0.06	0.60 ± 0.07	Not calculable

Table 2: Estimated 3 and 5 year survival rates ± SE and median overall survival after first vitreoretinal operation for Group A (SE=standard deviation).

Group / subgroup		N	Proportion surviving 3 years	Proportion surviving 5 years	Proportion surviving 10 years
Group A	All Patients	87	0.69 ± 0.06	0.49 ± 0.07	
	Diabetes mellitus type I	33	0.83 ± 0.08	0.71 ± 0.10	
	Diabetes mellitus type II	54	0.63 ± 0.07	<0.38	
	History of heart disease	36	0.51 ± 0.09	0	
	No history of heart disease	51	0.84 ± 0.06	0.81 ± 0.06	
	Treated with insulin	47	0.70 ± 0.08	0.49 ± 0.10	
	Not treated with insulin	40	0.68 ± 0.08	0.48 ± 0.09	
Group B	All Patients	145	0.91 ± 0.02	0.83 ± 0.03	0.68 ± 0.04
	Treated with diet only	58	0.93 ± 0.03	0.84 ± 0.05	0.74 ± 0.06
	Treated with oral hypoglycaemic agents	76	0.88 ± 0.04	0.80 ± 0.05	0.59 ± 0.06
	Treated with insulin alone	11	1.00	1.00	0.91 ± 0.09

Table 3: Mortality differences are shown in the form of probability of surviving, along with standard error where it is calculable. Blank cells indicate lack of relevant data.

This study has several strengths; it provides recent data and precise timing of survival for patients with diabetes undergoing vitrectomy in a UK regional surgical retina service. Furthermore, we have shown that patients undergoing vitrectomy for PDR are a very high risk group since 50% died within 5 years including all the patients with CHD. Although there is a big difference in severity between the 2 groups, this difference is not a weakness of the study but the main point. We believe that matching the two groups, if it were feasible, would be counterproductive, because the major differences in the state of health between vitrectomy patients and other patients with diabetes is what we are drawing attention to. The need for eye surgery is strongly associated with advanced disease as seen by high mortality, and a large part of the relevance of the findings is that such patients need more resources, more monitoring and more intensive management of their condition.

The aim of the study was not to claim a causal relationship. Even if we had claimed a causal relationship, the differences in age and sex and insulin treatment could not account for the difference in mortality. Our two groups had only a modest difference in sex ratio, whereas the difference in mortality rates was huge. The difference in the proportions being treated with insulin could not account for any of the mortality difference between the two groups either, because the relationship between treatment and mortality was in the wrong direction to explain our findings.

Limitations of this study include a possibility of selection bias, since patients and controls were selected at different time intervals. Also the number of patients and controls is relatively small compared to the high number of risk factors analysed. Lastly, by including patients operated in 2000 and 2006 only, the vitrectomy group may be inhomogeneous. However in our experience, treatment strategies were similar between these periods.

It is well recognised that the presence of PDR indicates advanced microvascular and macrovascular disease and is associated with reduced survival [5,6]. Data from follow up of patients in the Early Treatment Diabetic Retinopathy Study showed that the hazard ratio for the risk of mortality in patients with Type 2 diabetes increased from 1.37 for patients with

moderate non-proliferative retinopathy to 2.23 for patients with moderate to high risk PDR [10]. The same study also found a significantly increased risk of mortality in both Type 1 and Type 2 patients with macrovascular disease, neuropathy and nephropathy.

In our series, survival rates were lower compared to previous studies. Other studies have reported 5 year survival rates between 68% to 86% after vitreous surgery [4-9]. This difference might be associated with differences in social and healthcare provision, with Liverpool remaining one of the most deprived local authorities in England [11]. Additionally, a proportion of 48% of our vitrectomy group had known CHD at the time of surgery, which is higher than the 17-36% reported in other studies [4,6].

Gollamudi, et al. [5] evaluated 552 patients undergoing vitreous surgery for complications of DR and reported a 5-year survival rate of 74.7%. The presence of heart disease was not recorded but factors associated with shorter survival were older age, history of renal disease and longer duration of diabetes. As in our series, there was no association of survival rates with sex and type of treatment patients were receiving.

Helbig, et al. [6] reported 3- and 5-year survival rates for diabetic patients undergoing vitreous surgery of 83% and 68% respectively. In their series, age, heart disease and renal failure were statistically independent factors for survival with heart disease being the most important. In fact, heart disease was the only significant predictor for decreased survival in the subgroup of patients that had a diagnosis of diabetes before the age of 30. The median survival time of patients with heart disease after surgery was 3.5 years whereas the 5-year survival rate of patients without heart disease was 0.9. In our study, the corresponding figures were 3.4 years and 0.81 respectively. The mean age of patients and mean duration of DM were similar in both studies. In our study nephropathy was not associated with lower survival and this may be merely due to the fact that we did not use any strict criteria for its definition.

Banerjee, et al. [4] recently established 3-, 5- and 7-year survival rates of 94%, 86% and 77% respectively, in a UK group of 148 patients undergoing vitrectomy for PDR. Multivariate analysis showed increasing age, male sex and the presence of limb ulcers were independent negative prognostic indicators for survival. As in our study, CHD was also a significant negative predictor of survival. By using a control group, our study additionally highlights the decreased survival rate after vitrectomy, when compared to diabetic patients not requiring vitrectomy.

Despite advances in care, UK mortality rates in patients with diabetes continue to be much greater than in other chronic diseases [12,13], which continue getting the attention and funding from Primary Care Trusts and the government. Mortality rates continue to be greatly elevated: in the UK, annual mortality rates of 8.0 per 1,000 person-years have been reported in patients with Type 1 diabetes compared to 2.4 per 1,000 in the non-diabetic population [14]. For Type 2 DM, the annual mortality risk has been estimated to be approximately twice as high when compared with the general population [15].

This study shows that vitrectomy for diabetic retinopathy is a predictor of reduced life expectancy, particularly in the presence of cardiovascular disease. Although further prospective studies would be required to assess whether more intensive intervention will change the course of the disease, we strongly believe that patients with diabetes, when presenting to vitreoretinal clinics and requiring vitreous surgery, need particular attention. These patients have a 5 times higher death rate than patients not requiring posterior segment surgery. It is essential that vitreoretinal specialists and diabetologists develop a common care pathway for these patients. Vitreoretinal specialists should not only focus on the eye. Diabetologists must have a high level of awareness of the significance of vitrectomy for PDR. Both should consider working in closer proximity and also link closely with cardiologists. More trained nurses in the clinics are also required for better patient support. Our findings will be useful in counselling patients who are referred for vitreous surgery and in guiding public policy decisions regarding management of patients with diabetes.

Conclusion

It is well recognised that patients undergoing pars plana vitrectomy for complicated diabetic retinopathy are a subgroup of very ill patients. This study provides recent data and precise timing of survival for diabetic patients undergoing vitrectomy in a UK regional surgical retina service. It confirms that patients undergoing vitrectomy for PDR are a very high risk group, since 49% died within 5 years and none with heart disease were still alive. The findings from this paper will be useful in counselling patients referred for vitreous surgery, and in guiding public policy decisions regarding management of patients with diabetes.

Conflict of Interest

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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