

Outcome of Vitrectomy in Proliferative Diabetic Retinopathy Patients with Diabetic Nephropathy- A Retrospective Study at Tertiary Eye Centre, Telangana State, in South India

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ABSTRACT

BACKGROUND

The increase in prevalence of diabetes in India is one of the leading causes of blindness due to micro vascular and macro vascular complications. The complications in retina and kidney are due to damage of small vessels. Studies have shown significant association between diabetic retinopathy and diabetic nephropathy. In our study, we are discussing the complications during intra and post-operative period and also both anatomical and functional outcome in these patients after vitrectomy for proliferative diabetic retinopathy. Both eye and kidney share same vascular pattern. One pre-existing condition can be followed by the other condition due to similar microvascular damage. We wanted to evaluate the outcome of vitrectomy in proliferative diabetic retinopathy patients associated with chronic kidney disease.

METHODS

This is a retrospective study done at Sarojini Devi Eye Hospital, Telangana State, South India, over a two-year period from June 2017 to June 2019. Data was collected from old medical records of our institute, from patients who presented to Retina Dept. with various complaints. They were examined in detail, documented and treated based on clinical presentation after clearance from physician. Patients presented with different ocular manifestations like non-resolving vitreous haemorrhage, focal tractional retinal detachment, multi focal tractional retinal detachment like broad based, table top, combined retinal detachment and tractional maculopathy. Patients underwent pars plana vitrectomy with or without silicone oil endotamponade.

RESULTS

Prognosis in these patients was good only in cases of non-resolving vitreous haemorrhage and focal tractional retinal detachment (47.61%) whereas in cases like multifocal retinal detachment cases outcome was favourable (42.82%) but patients with combined retinal detachment (9.52%) had poor anatomical and visual outcome.

CONCLUSIONS

Management of these patients is very difficult when there is severe proliferative diabetic retinopathy with multiple broad vitreo retinal adhesions. Outcome is very poor particularly in patients of severe proliferative diabetic retinopathy associated with chronic kidney disease and coronary artery disease due to intra operative complications.

KEY WORDS

TRD (Tractional Retinal Detachment), VH (Vitreous Haemorrhage), PDR, DN (Diabetic Nephropathy), CABG, PPV, CRD (Combined Retinal Detachment), IOP, Focal, Multi Focal, Micro Albuminuria, Ranibizumab

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DOI: 10.14260/jemds/2020/155

*Financial or Other Competing Interests:
None.*

How to Cite This Article:

Sultana A. Outcome of vitrectomy in proliferative diabetic retinopathy patients with diabetic nephropathy- a retrospective study at tertiary eye centre, Telangana State, in South India. J. Evolution Med. Dent. Sci.2020;9(10):711-715, DOI: 10.14260/jemds/2020/155

*Submission 16-12-2019,
Peer Review 16-02-2020,
Acceptance 22-02-2020,
Published 09-03-2020.*



BACKGROUND

In Diabetic retinopathy the micro vascular complications due to uncontrolled glucose levels results in micro vascular damage, leading to break down of blood retinal barrier and micro circulation dysfunction. Uncontrolled hyperglycaemia will lead to hypoxia, expression of angiogenic growth factors, neovascularisation and proliferation. In Diabetic Nephropathy uncontrolled hyperglycaemia also causes changes in renal glomeruli like glomerular hypertrophy, hyper filtration due to hyperglycaemia in early stages; eventually increase in the intraglomerular pressure leading to thickening of glomerular and tubular basement membrane, accumulation of mesangial matrix and albuminuria.¹ Man et al. reported that a reduction in glomerular filtration rate (eGFR) is associated with increased severity of DR, but not with DME. Blood-sugar control together with tightly controlling blood pressure can reduce the risk of developing both DR and DN because the diseases share the same micro vascular changes.¹ The diabetic renal-retinal syndrome was defined as “coincident kidney and eye diseases resulting from diabetic microvasculopathy in retinal and glomerular arterioles and capillaries².

In our study we collected data of patients already who were diagnosed with severe proliferative retinopathy and kidney disease, all patients included in our study were on regular dialysis. Actually, we need to correlate the association of both retinopathy and nephropathy in diabetic patients of type 1 and type 2 diabetics, right from the beginning, we need to see the changes how they progress simultaneously and cause damage to retina and renal tissue with the uncontrolled hyperglycaemia. Many studies showed the duration of diabetes is related to the presentation of retinopathy and nephropathy in type 1 as well as youth onset type 2 diabetics patients, in our study all our patients were type 2 diabetics, I think the various factors which are responsible for the progression varies from person to person, only hyperglycaemia playing the critical role in progression of the micro vascular changes is still not clear according to literature. Genetic factors are also responsible for the progression of the retinopathy.

Possibly the genetic susceptibility is one of the main factors which will cause damage of both systems at different levels of glycemia and exposure to the other risk factors, so all patients will not have associated retinopathy and nephropathy. Identification of these genetic factors helps in preventing the disease in pre-clinical stage with appropriate management. In multivariable analyses, microalbuminuria remained statistically significantly associated with PDR in the younger but not the older onset group. Patients with type 1 diabetes, the annual incidence of PDR in persons with early nephropathy was 10–15% compared with only 1% in patients without signs of nephropathy.

Common Risk Factors

Hyperglycaemia, hypertension, and dyslipidaemia, shown to be related to the incidence of diabetic nephropathy. Other risk factors, such as high levels of markers of inflammation, endothelial dysfunction, oxidative stress, and

hypercoagulability have also been shown in some studies to be related to both retinopathy and nephropathy.³ The presence and severity of diabetic nephropathy is usually clinically characterized by functional changes such as increased albumin excretion and decreased creatinine clearance. Pars plana vitrectomy in these cases especially multi focal tractional retinal detachment cases results are not much favourable because diffuse ischemic retina and florid vascularised membranes, broad based vitreo retinal adhesions will cause multiple iatrogenic retinal breaks and profuse intra operative bleed. Viewing also becomes difficult due to continuous bleed. Immediate post-operative bleed, noted in few cases, they had elevated serum creatinine and other macro vascular events.

We wanted to evaluate the surgical outcome in patients with severe proliferative diabetic retinopathy associated with nephropathy.

METHODS

This is a retrospective study conducted at Vitreo Retina Dept., Sarojini Devi Eye Hospital, Telangana state, South India.

Inclusion Criteria

- Proliferative diabetic retinopathy patients with associated chronic kidney disease.
- Both type 1 and 2 diabetic patients.
- All patients irrespective of any age.
- Patients with other systemic co morbidities.

Exclusion Criteria

Proliferative diabetic retinopathy patients with no history of kidney disease. Kidney disease patients with no diabetic retinopathy.

21 patients of severe proliferative diabetic retinopathy with associated kidney disease at various stages presented to our vitreo retina dept. from June 2017 to June 2019. All these patients underwent detailed ocular and systemic examination. BCVA, Slit lamp examination, fundus examination by indirect ophthalmoscopy, if media hazy b scan, documentation, systemic examination like GFR, urine sugar and albumin, haemoglobin levels, HbA1C, blood urea, serum creatinine, if patient had cardiac problem, ECG, 2D ECHO, cardiologist opinion for vitreo retinal surgery, to stop blood thinners one week before surgery. Patients who were on dialysis, advised to go for heparin free dialysis one day prior to surgery, with the help of physician clearance, surgery planned under monitoring of anaesthetist. With the control of all parameters, patient consent taken for surgery after explaining the prognosis. Patients were injected intra vitreal anti VEGF prior surgery. Patients underwent pars plana vitrectomy based on the clinical presentation, if required silicone oil was injected and removed after three months.

Statistical Analysis

The data was analyzed using SPSS 21.0 version. All the variables were calculated in numbers and percentages.

RESULTS

Clinical Presentation	No. of Cases	Best Corrected Visual Acuity
Non-resolving VH	4(19.04%)	6/18-6/24
VH + Focal TRD	6(28.57%)	6/24-6/36
VH + Multifocal TRD	4(19.04%)	6/60-3/60
Multi focal TRD involving macula	3(14.28%)	2/60
Combined RD +VH	2(9.5%)	3/60
Combined RD	1(4.76%)	1/60
Combined RD	1(4.76%)	NPL

Table 1. Number of Patients Who Presented with Various Clinical Manifestations

Post-Operative Complications	No. of Cases
Haemorrhage in vitreous cavity	2(9.5%)
Iatrogenic Retinal breaks	2(9.5%)
Residual retinal detachment	1(4.7%)
Hyphaema	2(9.5%)
Raised IOP	2(9.5%)

Table 2. Percentage of Patients Who Presented with Intra- and Post-Operative Complications

DISCUSSION

Association of kidney disease in diabetic proliferative retinopathy is a significant factor for the prognosis. Other systemic co morbidities also have risk for poor outcome. Factors like hypertension, CAD (coronary artery disease), hyperlipidaemia are major factors which are responsible for outcome. Patients with acute and chronic kidney disease are included in our study. All of our patients were on dialysis, serum creatinine levels were maintained, and opinion obtained from nephrologists for further management. Male gender was predominantly noted, only one or two females were reported, all our patients were type 2 diabetic patients and age of presentation was between 40 to 50 years. Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria, arterial blood pressure elevation, decline in glomerular filtration rate (GFR), and a high risk of cardiovascular morbidity and mortality. This major life-threatening complication develops in approximately 20% to 40% of type 1 and less than 20% of type 2 diabetic patients².

In our study we did not noted the incidence of people presented with kidney disease, more than 2 to 3 patients out 10 to 12 patients of diabetic history, present with severe proliferative diabetic retinopathy every day to our department. Total number of patients per year will be more than 1800. Diabetic screening is done in all patients presented with history of diabetes, irrespective of duration of disease. In the same manner patients who are presenting to nephrologists are missed for retinopathy examination, all patients presenting for retinopathy should be advised for at least urine albumin examination frequently to exclude diabetic nephropathy. Diabetic nephropathy can present in any form like nephritis, nodular glomerular sclerosis. Initial stages of kidney diseases can be managed by diet therapy. In 1936, Kimmelstiel and Wilson described the renal histology at autopsy in eight cases of which seven had diabetes, together with hypertension, albuminuria, oedema, and renal failure and had the characteristic nodular lesions of diabetes mellitus.² One third of diabetic population has nephropathy, nephropathy is related to the duration of diabetes in youth

onset type 2 diabetics (more than 20 years), whereas retinopathy was not related to duration of diabetes in youth onset type 2. Retinopathy was commonly noted in adult onset type 2 diabetics.⁴

In our study most of the nephropathy patients were adult onset type 2 diabetic patients, presented with severe proliferative diabetic retinopathy. Most important other factor associated in our patients was cardiovascular disease. Diabetic glomerular injury is related to the duration of the diabetes. Proteinuria increases the mortality in all types of diabetic patients. In our study type 1 young patients were reported with kidney disease were less than type 2 patients. Youth onset type 2 diabetes patients in our study were presented with initial stages of kidney disease with severe proliferative retinopathy in both eyes⁵ Rani et al, in their study³ suggested that the association between microalbuminuria and DR could be explained by the fact that micro albuminuria might represent a state of generalized vascular dysfunction; in our study also most of our patients had cardio vascular events history. Diabetic nephropathy was diagnosed based on the presence of albuminuria (micro albuminuria defined as urine albumin-creatinine ratio of 30-299 mg/g Cr or macro albuminuria defined as albumin-creatinine ratio \geq 300 mg/g Cr) and/or reduced estimated Glomerular Filtration Rate (eGFR) $<$ 90 ml/min/m.³

Diabetic nephropathy develops in 40% of type 2 diabetic patients, characterized by persistent albuminuria. Progression to micro albuminuria occurs at 2.0% per year, and about 25% of patients with diabetes develop micro albuminuria or worse nephropathy within 10 years of diagnosis.⁶ Patients underwent 20- and 23-gauge pars plana vitrectomy under monitoring of anaesthetist with all parameters under control. Intra operative complications were mostly active bleed, which was controlled with increasing infusion pressure, heavy liquids and also by fluid air exchange, formation of blood clots on retina and risk of retinal breaks were commonly noted in few cases due to ischemic retina. Post-operative complications were lyses of clot causing dense haemorrhage in vitreous cavity, hyphaema, raised intra ocular pressure and proliferative vitreo retinopathy in cases of combined retinal detachment. In cases of combined retinal detachment due to vitreo schisis, any part of the residual vitreous in the periphery can proliferate and cause retina lift leading to retinal detachment. In these cases, second procedure required to flatten retina by releasing traction or adhesions from retina. After vitrectomy patients were followed for three months. Follow ups were on first post-operative day, one week, 2 weeks, 4 weeks, 8 weeks and 12 weeks. Anti VEGF was given in every patient to avoid all these complications, but active bleed still occurred in all these cases. After 12 weeks, BCVA, slit lamp examination, fundus examination and documentation done. Laser was completed if any skip areas noted, silicone oil removal done.

Patients with heparin free dialysis one day prior surgery and patients where dialysis stopped one day before surgery were compared to see the outcome in both the groups, patients with heparin free dialysis were 5 patients and patients without dialysis one day before surgery were 5 cases. Outcome was same in both groups, both anatomically and functionally, there was no difference in severe PDR cases like multi focal tractional retinal detachment and combined retinal detachment. In non-resolving VH and Focal TRD, cases

we advised to stop dialysis one day before surgery, outcome was good, possibly retinopathy is not severe. Outcome of vitrectomy is mainly based on the extent of vitreo retinal adhesions and also the vascularity of the membranes.⁷ Pre-operative anti VEGF was given in all cases; Ranibizumab was given to minimise surgical complications and improve surgical outcome. Ranibizumab is a humanized monoclonal antibody fragment, which lacks an Fc domain, that functions by blocking all VEGF-A isoforms.⁸ Two groups were compared to see the outcome. According to some authors the use of anti VEGF agents there is no role in the outcome of vitrectomy in PDR cases⁹. In our study not only the active bleed, risk of resurgery was also reduced, hence anti VEGF agents are safe and effective in favourable outcome. Some studies showed that pre-operative anti VEGF agents also minimise the silicone endotamponade, which can cause cataract and requires removal of silicone later. In our study except four cases of VH, silicone endotamponade used in all other cases. Anti VEGF agents maintain haemostasis and helps in reintegration of retinal vascular tissue.

We also compared two groups, one group was operated 2 days after anti VEGF injection and other group was operated one week after surgery, though final outcome was almost same in both the groups but immediately after surgery on first post-operative day group 2 that is patients who were operated one week after injection showed good anatomical outcome compared to group1, where patients were operated two days after injection. 3 patients were operated in each group, anti VEGF used was in our study was Ranibizumab in all patients, intra ocular half-life of Ranibizumab is 7.2 days in human eyes, in non vitrectomised eyes, probably this could be the reason for the good outcome in group 2 patients. Though anti VEGF regresses the new vessels and reduces the active intra operative bleed, presentation of retinopathy and severity of nephropathy is very important prognostic factor. Outcome of surgery with anti VEGF prior to surgery also compared with patients of diabetic nephropathy free disease, here also patients who were operated one week after anti VEGF injection showed good anatomical outcome immediately first day after surgery compared to patients who were operated 2 days after anti VEGF injection. Anti VEGF injection will definitely help in regression of the active vascularity, but in patients where early vitrectomy planned, 2 days after injection of ranibizumab will have risk of intra operative bleed compared to patients where vitrectomy planned one week after injection, particularly in cases like multi focal and combined retinal detachment.

Though few studies showed favourable outcome, our study revealed poor outcome in severe proliferative diabetic patients with nephropathy, reason could be poor glycaemic control, micro and macro vascular dysfunction. Impact of micro albuminuria is always there on retinopathy and outcome.¹⁰ BCVA mentioned in our study were after removal of silicone oil. Elevated urinary albumin excretion has been found to increase the risk of proliferative diabetic retinopathy (PDR) and is associated with a higher prevalence of PDR.¹¹ In our study we used only silicone oil tamponade, gas was not used, and there was hyphaema in two cases after surgery, probably diffusion of lyses blood in to anterior segment. IOP was raised and caused severe discomfort to patient. We need to exclude ocular co morbidity like neo vascular glaucoma to explain the prognosis before surgery.

Gonioscopy and slit lamp examination of iris are very important predicting factors for the anatomical and functional outcome. PFCL (per fluorocarbon liquids, heavy liquids) used to prevent retinal breaks while peeling membranes and for haemostasis. Some studies showed corneal epithelial damage following vitrectomy in nephropathy cases, we observed these changes in patients with high serum creatinine levels, two patients in our study showed epithelial damage, one patient had serum creatinine 5.9 mg/dl and other patient had 7.3 mg/dl even after regular dialysis. Patients with abnormal renal profile will have excessive release of vascular endothelial growth factors which may be responsible for poor outcome.

CONCLUSIONS

Management and outcome of pars plana vitrectomy in proliferative diabetic retinopathy with nephropathy has poor anatomical and functional outcome if presentation of patient is delayed. Prognosis is good only when the retinopathy is not advanced. Screening in diabetics is done regularly to identify the retinopathy; in the same way regular monitoring of kidney function is also very important to prevent the progression of retinopathy in these patients. Kidney disease in early stages is usually asymptomatic; so, most of the diabetic nephropathy cases are missed and patients are presenting in the end stage with severe nephropathy and retinopathy. Most of our patients also had cardiovascular disease, macro vascular dysfunction due to chronic kidney disease. Most of our patients, nearly 70 to 80 percentages had history of cardiac disease, who had undergone angioplasty (40%) or coronary artery bypass graft (60%) (CABG). These patients were referred to cardiologist for fitness and also for opinion to stop blood thinners for 5 to 7 days prior surgery to reduce the risk of intraoperative and post-operative bleed. Extent of retinal detachment, fibro vascular proliferation with active or inactive neovascularisation, iris neovascularisation and long-standing atrophic thinning of macular detachment and associated systemic diseases were poor prognostic factors.

Limitations

As all patients in our study were already on dialysis due to chronic kidney disease, we have not screened our patients to assess kidney function. Small sample size is another limiting factor. All our diabetic retinopathy cases should be followed for timely evaluation of renal status to detect the early kidney dysfunction, so that we can study the incidence of nephropathy in our patients at early stage. Regular urine examination for microalbuminuria, to identify the diabetic glomerular injury helps to control the progression of retinopathy, because nephropathy progresses retinopathy rapidly. Micro albuminuria is reliable predictor, simple marker which helps to screen all diabetic patients to assess renal status when patient comes for regular follow up. We have used only Ranibizumab anti VEGF agent before surgery in all cases; other anti VEGF agents which are available were not used and compared with the surgical outcome.

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