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Original Research Article

Comparison of eGFR Levels in Patients Before and After Intravitreal Bevacizumab (Anti-VEGF) Injection

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Abstract

Background: Estimated glomerular filtration rate (eGFR) is a vital indicator of kidney function, particularly in patients receiving treatments that may impact renal health, such as intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections like bevacizumab. Bevacizumab, commonly used to treat retinal diseases like diabetic retinopathy, has raised concerns about its potential systemic effects, including its impact on kidney function due to the role of VEGF in maintaining glomerular integrity. This study investigates the effect of bevacizumab injections on renal function in patients with diabetic kidney disease (DKD) and those without. ***Objective:*** To assess changes in eGFR before and after intravitreal bevacizumab injections in patients with and without diabetic kidney disease, evaluating whether these injections significantly affect renal function. ***Methodology:*** This quasi-experimental study was conducted in the Department of Ophthalmology, Bangabandhu Sheikh Mujib Medical University (BSMMU), from April 2019 to August 2021. Forty patients with diabetic retinopathy were selected, divided equally into DKD and non-DKD groups. Serum creatinine and eGFR were measured within 30 days before the injection and one month after the third dose of intravitreal bevacizumab. eGFR was calculated using the CKD-EPI equation, and statistical analysis was performed using SPSS. ***Results:*** The mean pre-injection eGFR was 69.35±25.91 ml/min/1.73m² in the DKD group and 96.7±30.59 ml/min/1.73m² in the non-DKD group. Post-injection, the mean eGFR was 73.3±33.87 ml/min/1.73m² in DKD patients and 93.6±29.7 ml/min/1.73m² in non-DKD patients. The mean differences in eGFR were not statistically significant between pre- and post-injection measurements in either group ($p>0.05$). ***Conclusion:*** Intravitreal bevacizumab injections did not cause significant changes in eGFR in both DKD and non-DKD patients, suggesting that the treatment is unlikely to have a detrimental impact on renal function in the short term. Further studies are needed to assess the long-term effects of repeated injections.

Keywords: eGFR, intravitreal bevacizumab, diabetic retinopathy, diabetic kidney disease, anti-VEGF, renal function, systemic effects.

INTRODUCTION

The estimated glomerular filtration rate (eGFR) is a critical indicator of renal function and is used to assess how well the kidneys filter waste from the blood. It serves as an essential marker in monitoring overall kidney health, especially in clinical settings where nephrotoxic agents or treatments that may affect renal function are used [1-3]. Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents, such as bevacizumab, are widely used in the treatment of retinal diseases such as age-related macular degeneration (AMD), diabetic retinopathy, and retinal vein occlusion. While these agents have shown significant efficacy in preserving and improving vision, their systemic effects,

particularly on renal function, remain a subject of growing interest and study [4-5].

Bevacizumab is a monoclonal antibody that inhibits VEGF, a protein that promotes angiogenesis and increases vascular permeability. By blocking VEGF, bevacizumab reduces abnormal blood vessel formation and leakage in retinal tissues. Although its primary effect is local when injected intravitreally, there is potential for systemic absorption and distribution, raising concerns about its impact on other organs, including the kidneys [6-7]. VEGF plays a crucial role in maintaining the health of glomerular endothelial cells and podocytes in the kidney. Thus, inhibition of VEGF could, in theory, affect renal function, particularly in patients who already have compromised kidney function [8].

This study aims to assess the effect of intravitreal bevacizumab injections on renal function, as measured by eGFR, in patients undergoing treatment for retinal diseases. By comparing eGFR levels before and after the administration of bevacizumab, we seek to determine whether there are significant changes in kidney function that could suggest systemic effects of the drug. The study population consists of patients who have undergone multiple intravitreal injections, providing a valuable dataset for understanding the potential cumulative effects of this treatment on renal health.

In the clinical management of patients with retinal diseases, especially those with coexisting conditions like diabetes or hypertension, monitoring renal function is essential. These patients often have pre-existing renal impairment, making it particularly important to understand the safety profile of treatments like bevacizumab. Even subtle changes in eGFR after treatment could have long-term implications for patient care, especially in populations at risk for chronic kidney disease (CKD).

Thus, this study contributes to the growing body of evidence examining the systemic safety of anti-VEGF therapy. By focusing on eGFR, an easily accessible and reliable marker of kidney function, the findings may provide important insights for clinicians in tailoring treatment plans, particularly in patients with pre-existing renal conditions or those at higher risk of renal impairment. Understanding whether bevacizumab affects renal function could guide the frequency of injections, the need for additional monitoring, and potential alternative treatments for at-risk patients.

Objective

The outcomes of this study will help clarify the relationship between intravitreal bevacizumab administration and renal function, contributing to safer, more effective treatment protocols for patients with retinal diseases requiring anti-VEGF therapy.

METHODOLOGY

Type of Study: Quasi experimental study

Place of Study: Sheikh Fazilatunnessa Mujib Eye Hospital and Training Institute, Gopalganj

Study Population: The patients with diabetic retinopathy treated with intravitreal injection bevacizumab attending in the department of ophthalmology, BSMMU.

Period of Study: The study was conducted from April, 2022 to August, 2023

Sampling Technique: Purposive sampling technique was applied to collect the sample from the study population.

Selection Criteria:

Inclusion Criteria:

1. Any patient of diabetic retinopathy undergoing intravitreal injection of anti VEGF.
2. Patient having Diabetic Kidney Disease (DKD) or not
   DKD- if UACR $\geq$ 30 mg/g or
   eGFR < 60mL/min/1.73m^2
   No DKD- if UACR < 30 mg/g or
   eGFR $\geq$ 60mL/min/1.73m^2
3. Patient of both sex.
4. Age >18 yrs.

Exclusion Criteria:

1. Patient who had intravitreal injection of anti-VEGF any time up until 6 month prior to the study.
2. Patient with other ocular disease.
3. Patient with end stage renal disease (receiving hemodialysis or eGFR $\leq$15mL/min/1.73m^2).
4. One eyed patient.
5. Pregnant or lactating women.

Sample Size: The sample size has been determined by using following formula:

$$\frac{(u+v)^2(\sigma_1^2+\sigma_0^2)}{([\mu_1-\mu_0])^2}$$

Two sided two sample unequal variance t-test

u = 0.842

v = 1.96

$\mu_1 = 75.7$

$\mu_0 = 57.1$

$\sigma_1 = 15.6$

$\sigma_0 = 24.6$

μ_1 and μ_0 are the assumed population means for power and sample size calculations.
$\mu_1 - \mu_0$ is the difference between population means for at which power and sample size calculations are made. μ_1 and μ_0 are the assumed population standard deviations for group 1 and 2, respectively
Using the above formula the expected sample size.

$$N = \frac{(0.842+1.96)^2\,(15.6^2+24.6^2)}{(75.7-57.1)^2} = 19.25628$$

Sample size was 20 for each group.

Study Procedure and Design

Patients attending the Department of Ophthalmology, Bangabandhu Sheikh Mujib Medical University, who are diagnosed as a case of diabetic retinopathy with or without nephropathy undergoing intravitreal injection of bevacizumab of either sex was evaluated for renal function (S. creatinine, eGFR, UACR) done within 30 days before the injection and 1 months after 3rd dose of injection.

Intravitreal injection of bevacizumab was performed with aseptic technique in ophthalmology operation theatre in BSMMU. The intravitreal dose of bevacizumab was 1.25mg/0.05ml and given 1monthly by multiple vitreo-retina specialists. Patients were prepared and drapped in a standard fashion and supine position for procedure. After applying topical proparacaine for anesthesia lid speculum was used for lid control and the eyeball was sterilized with 5% povidone-iodine and irrigated with sterile BSS, injection was injected with 30 guage needle through the supero-nasal pars plana 4 mm for phakic and 3.5 mm for pseudo phakic, posterior to the limbus. The needle inserted approximately 1.0 cm into the globe, and the injection was performed. Sterile cotton swab was placed on the injection site to prevent reflux of the medicine or vitreous.

All three biochemical investigations (Serum Creatinine, eGFR and UACR) were done in the Department of Biochemistry and Molecular Biology, Bangabandhu Sheikh Mujib Medical University.

Serum Creatinine was measured with the help of the machine named Siemens Healthineers (Atellica CH analyzer). Sample volume of serum was 24 microlitre. Here combined reagent was used that is R1-17 ml & R2-17 ml.

eGFR was measured by an equation developed by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration.

eGFR= $186 \times (\text{S. Creatinine})^{-1.154} \times (\text{Age})^{-0.203}$ ($\times 0.742$ if female) (Levey *et al.*, 2009).

To measure Urinary Albumin Creatinine Ratio (UACR), at first urinary creatinine & urinary albumin are measured separately. Then UACR was measured by the following equation-

UACR= Urinary micro-albumin × 100 ÷ Urine creatinine

Urinary creatinine measurement is as that of serum creatinine & urinary albumin was measured with the machine named Siemens Healthineers (Atellica CH analyzer). Sample volume 13.7 micro-litre. Combined reagent is used here (R1-14.0ml & R2- 4.3 ml) & the test duration is 10 minutes.

The purpose of the study is to investigate the effect of intravitreal antivascular endothelial growth factor (VEGF) injection on renal function.

The purposive sampling technique was applied to collect sample from the study population as per inclusion and exclusion criteria.

Complete clinical evaluation including history, physical examination, relevant ocular examination was done in the department of ophthalmology, Bangabandhu sheikh Mujib Medical University.

Data Collection, Processing& Analysis:

The demographic information relevant history, examination findings, investigation report and fundus examination of all the study participants were recorded in the data collection sheet.

Data analysis plan:

After completion, the data was presented in the form of tables, figures and graphs, as necessary. Statistical analysis of the result was done by using computer based software, SPSS (SPSS in, Chicago, IL, USA-25). Descriptive statistics: Mean, SD, Frequency and Percentage. A probability "P" value of 0.05 or less considered as significant.

RESULTS

Bar diagram showing the distribution of the study patients by age. It was observed that half (50.0%) patients belonged to age 50-59 years in DKD and more than half that is (65.0%) in No DKD. 25% Patients with DKD and 5% patients with no DKD belongs to the age group of <50 years. 15% Patients with DKD and 25% patients with no DKD belongs to the age group of 60-70 years and 10% Patients with DKD and 5% patients with no DKD belongs to the age group >70 years.

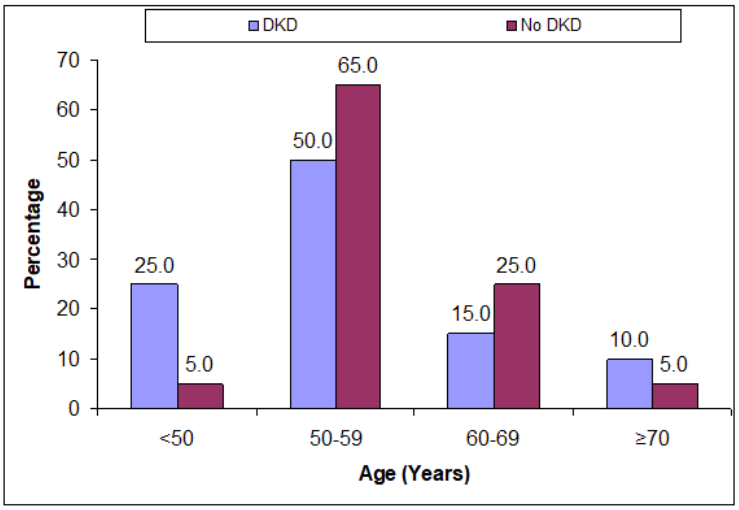

Figure-1: Bar diagram showing distribution of the study patients by age (n=40)

Pie chart showing 13 patients that is 65% were male and 7 patients that is 35% were female among DKD group.

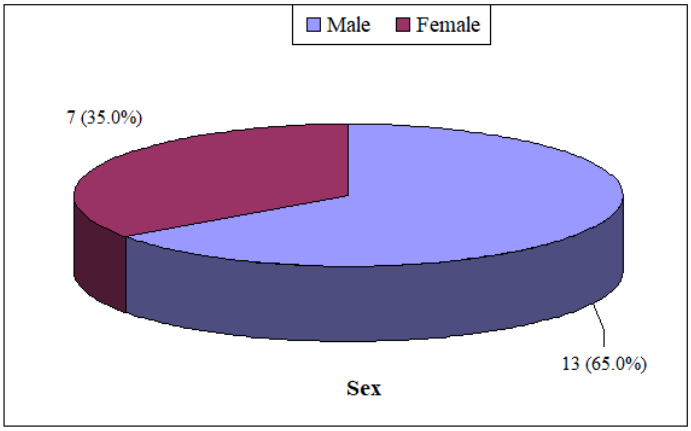

Figure-2: Pie chart showing distribution of the DKD patients by sex (n=20)

Pie chart showing 14 patients that is 70% were male and 6 patients that is 30% were female among No-DKD group.

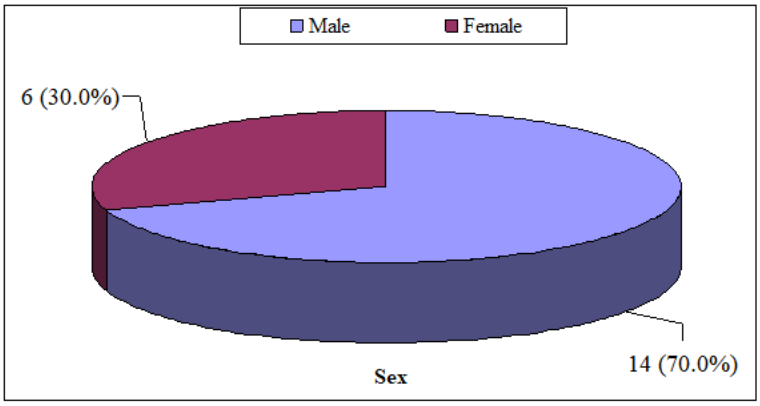

Figure-3: Pie chart showing distribution of the No-DKD patients by sex (n=40)

The mean pre-injection of eGFR was 69.35±25.91 ml/min/1.73m2 in DKD and 96.7±30.59 ml/min/1.73m2 in No DKD. The mean post-injection of eGFR was 73.3±33.87 ml/min/1.73m2 in DKD and 93.6±29.7 ml/min/1.73m2 in No DKD. The mean difference of eGFR was not statistically significant (p>0.05) between pre-injection and post-injection in both groups.

Table I: Distribution of the study patients by pre-injection and post-injection with eGFR (n=40)

eGFR (ml/min)	**DKD (n=20)**		**No DKD (n=20)**	
	Mean±SD	**Range(min-max)**	**Mean±SD**	**Range(min-max)**
Pre-injection	69.35±25.91	27-116	96.7±30.59	64-164
Post-injection	73.3±33.87	39-147	93.6±29.7	60-164
p value	0.508^{ns}		0.619^{ns}	

ns= not significant
p value reached from Paired t-test

DISCUSSION

In this study, we examined the effect of intravitreal bevacizumab injections on renal function, specifically measuring the pre- and post-injection eGFR in patients with and without diabetic kidney disease (DKD). We compared our results to previous studies exploring similar effects, noting both similarities and dissimilarities in findings across different patient groups and methodologies. [9-11] Additionally, we analyzed the distribution of study patients by age and gender, revealing potential demographic patterns related to the study outcomes.

One of the primary similarities between our study and previous research is the finding that intravitreal bevacizumab injections do not result in significant changes in eGFR. Several studies have reported that systemic absorption of bevacizumab is minimal when administered intravitreally, leading to no significant renal impairment in patients post-injection. [12-13] Our findings align with this, as we observed no statistically significant differences in eGFR between pre- and post-injection measurements in both the DKD and non-DKD groups. The p-values in our study (p = 0.508 in DKD, p = 0.619 in non-DKD) corroborate the overall consensus that intravitreal anti-VEGF injections have a negligible impact on renal function.

However, a key difference from some studies is the demographic profile of our patients, particularly regarding age distribution. As shown in the bar diagram (Figure 1), 50% of patients with DKD were aged 50-59, while a higher proportion (65%) of non-DKD patients fell into this age group. Other studies often report a more evenly distributed age range or focus more on elderly populations, particularly those over 60 years old, who may be at higher risk of both retinal diseases and renal impairment. [14] Our study had fewer patients in the older age groups (15% in DKD and 25% in non-DKD for those aged 60-70), which could influence the generalizability of our findings, especially concerning older individuals who might be more susceptible to renal dysfunction.

In terms of gender distribution, our study found that 65% of patients in the DKD group were male, and 35% were female, as illustrated by the pie chart (Figure 2). This male predominance is consistent with several studies that report higher rates of DKD and diabetic complications among men. However, some studies have observed a more balanced gender distribution or even a slight female preponderance in cases of retinal diseases treated with anti-VEGF therapy. [15] This gender skew in our study could be an influential factor in the eGFR outcomes, as renal function changes and susceptibility to systemic effects of medications might vary between genders due to physiological differences.

Regarding the baseline eGFR values, the pre-injection mean eGFR in our study was 69.35±25.91 ml/min/1.73m² for DKD patients and 96.7±30.59 ml/min/1.73m² for non-DKD patients. While these values are consistent with expected renal function levels in populations with and without diabetic kidney disease, the wider range of eGFR in the DKD group (27-116 ml/min/1.73m²) suggests more heterogeneity in kidney function among these patients compared to non-DKD patients. Some studies have found a more homogeneous renal function profile in diabetic patients undergoing bevacizumab treatment, which may reflect differences in patient selection criteria or the severity of DKD in the populations studied. [16]

Finally, while our study did not find significant changes in eGFR post-injection, some research suggests that long-term or repeated anti-VEGF injections could potentially lead to cumulative effects on kidney function. Our study focused on short-term eGFR changes after a single injection, and thus, it is possible that prolonged treatment could yield different outcomes. Future research with longer follow-up periods and repeated eGFR measurements could offer a more comprehensive understanding of the potential renal implications of ongoing anti-VEGF therapy.

CONCLUSION

In conclusion, our findings are largely consistent with previous research in demonstrating that intravitreal bevacizumab injections do not significantly affect renal function in the short term, as measured by eGFR.

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