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Effect of Intravitreal Bevacizumab (Anti VEGF) Injection on Renal Function

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Abstract

Background: Vascular endothelial growth factor (VEGF) plays an important role in the development of both Proliferative Diabetic Retinopathy (PDR) & Diabetic Macular Odema (DMO). An intravitreal anti-VEGF agent is an effective new modality of treatment. Some studies have dealt with systemic effects of intravitreal injection of anti-VEGF. However, decreasing renal function has been reported recently. ***Aims:*** To investigate the effect of intravitreal bevacizumab (anti VEGF) injection on renal function. ***Methods:*** This quasi-experimental study was carried out in the Department of ophthalmology, Bangabandhu Sheikh Mujib Medical University, Dhaka, during March 2019 to August 2021. A total of 40 patients with retinopathy treated with intravitreal injection bevacizumab were included in this study, out of which 20 patients having diabetic kidney disease (DKD) and rest 20 patients without diabetic kidney disease (No DKD). The patients having Diabetic Kidney Disease (DKD) whose Urinary Albumin Creatinine Ratio (UACR) > 30 mg/g or Effective Glomerular Filtration Rate (eGFR) < 60mL/min/1.73m^2, No Diabetic Kidney Disease (No DKD) whose UACR < 30 mg/g or eGFR > 60mL/min/1.73m^2. Patients of both sexes and age above 18 years were enrolled in this study. Pre- injection and 1 month after 3rd dose of intravitreal injection of bevacizumab, UACR, Serum Creatinine and eGFR were measured and compared. ***Results:*** It was observed that half (50.0%) of the patients in DKD and more than half (65.0%) in No DKD belonged to age group 50-59 years. Male was predominant in both the groups. The mean pre-injection of serum creatinine was 1.23±0.53 mg/dl in DKD and 0.87±0.22 mg/dl in No DKD. The mean post-injection of serum creatinine was 1.19±0.45 mg/dl in DKD and 0.87±0.16 mg/dl in No DKD. The mean pre-injection of UACR was 1294.9±968.26 mg/g in DKD and 13.8±5.99 mg/g in No DKD. The mean post-injection of UACR was 1142.11±1024.06 mg/g in DKD and 13.01±6.87 mg/g in No DKD. The mean difference of serum creatinine, eGFR and UACR were not significant (p>0.05) between pre-injection and post-injection in both groups. ***Conclusion:*** Serum creatinine, eGFR and UACR were almost similar between pre-injection and post-injection in patients with diabetic kidney disease (DKD) and patients without diabetic kidney disease (No DKD).

Keywords: Bevacizumab, Diabetic Kidney disease., Renal function.

INTRODUCTION

VEGF plays an important role in maintaining normal kidney function. VEGF discharged from podocytes interacts with VEGF receptor 2 on glomerular capillaries and advances keenness of endothelial fenestrations and resultant glomerular barrier function[1].

A systematic survey and meta-analysis of 1850 patients over seven clinical trials uncovered a critical dosage subordinate increment in chance related with hypertension and proteinuria in those getting intravenous bevacizumab [2].

Persistent hyperglycemia as a result of diabetes mellitus (DM) has been shown to activate abnormal

metabolic pathways that trigger a complex cascade of inflammatory and vasogenic rea VEGF may be a major driver within the pathophysiology of DMO because it advances retinal angiogenesis and capillary hyper-permeability that can disturb the inner blood retinal barrier, resulting accumulation of fluid into the retinal tissue. DMO is one of the main causes of vision loss in adults [3]. Intravitreal VEGF inhibitors have become an integral part of treatment of this disease.

Proliferative diabetic retinopathy (PDR) is one of the foremost imperative microvascular complications among the patients with diabetes. Researchers reported that Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agent enacts a key role in PDR [4]. They also concluded that intravitreal bevacizumab injection was not associated with renal dysfunction and proteinuria in patients with diabetic nephropathy.

It is anticipated that fast increment in DM predominance will result in a parallel increment in diabetic microvascular complications including diabetic retinopathy and nephropathy reinforcing the require for rigid security assessment of intravitreal anti-VEGF treatments.

The intravitreal injection of anti-angiogenic agents (bevacizumab) becomes a more common treatment modality for various vitreo-retinal diseases. However, it could decrease the plasma VEGF level & the subsequent side effects may occur. Podocytes express VEGF that interact with VEGF receptor-2 on glomerular capillary endothelial cells to keep normal renal function. Inhibition of VEGF leads to endothelial fenestrations & proteinuria [5].

Objective

To asses effect of intravitreal bevacizumab (anti VEGF) injection on renal function.

METHODOLOGY

Type of study: Quasi experimental study

Place of study: Department of Ophthalmology, Bangabandhu Sheikh Mujib Medical University (BSMMU).

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, 2019 to August, 2021

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 ≥ 30 mg/g or
   eGFR < 60mL/min/1.73m^2
   No DKD- if UACR < 30 mg/g or
   eGFR ≥ 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 ≤15mL/min/1.73m^2).
4. One eyed patient.
5. Pregnant or lactating women.

Sample Size:

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

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.

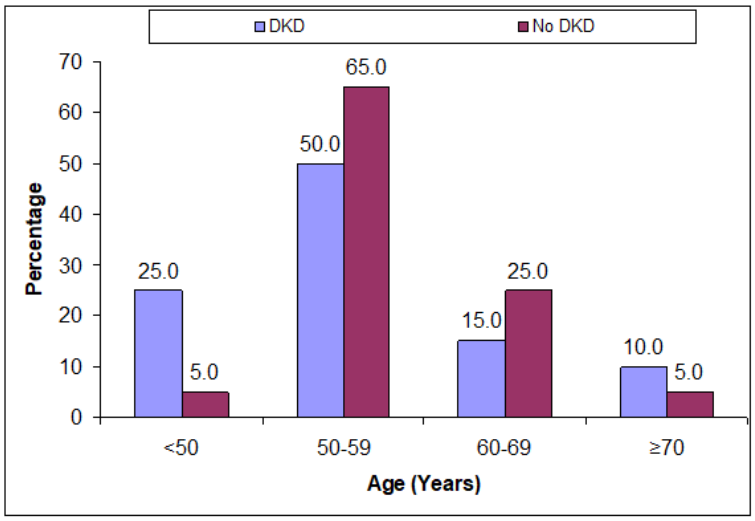

Figure-1: Bar diagram showing distribution of the study patients by age (n=40)

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

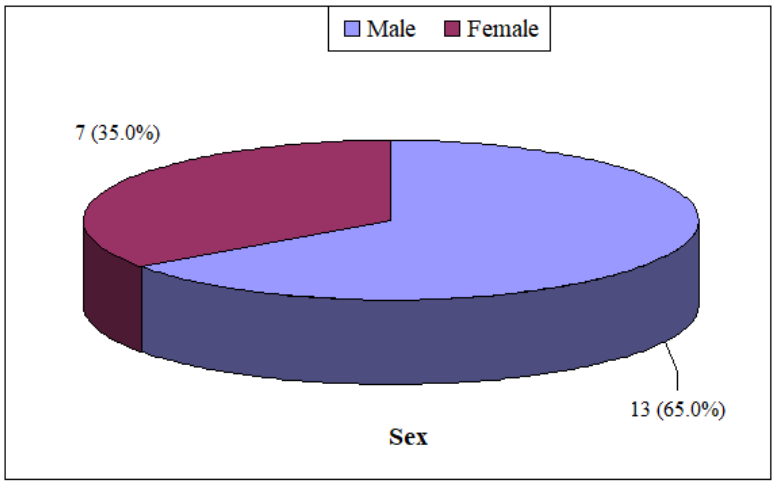

Figure-2: Pie chart showing distribution of the DKD patients by sex (n=20)

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

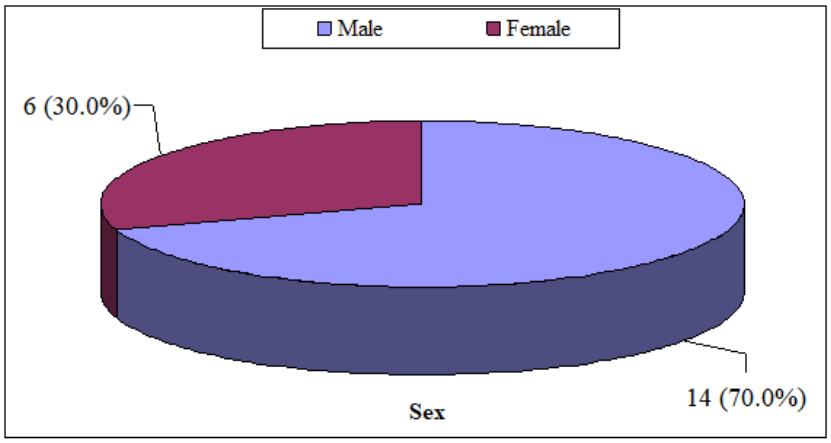

Figure-3: Pie chart showing distribution of the No-DKD patients by sex (n=40)

The mean pre-injection of serum creatinine was 1.23±0.53 mg/dl in DKD and 0.87±0.22 mg/dl in No DKD. The mean post-injection of serum creatinine was 1.19±0.45 mg/dl in DKD and 0.87±0.16 mg/dl in No DKD. The mean difference of serum creatinine level was not 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 serum creatinine (n=40)

S. creatinine (mg/dl)	DKD (n=20)		No DKD (n=20)	
	Mean±SD	Range(min-max)	Mean±SD	Range(min-max)
Pre-injection	1.23±0.53	0.72-2.41	0.87±0.22	0.48-1.25
Post-injection	1.19±0.45	0.48-1.93	0.87±0.16	0.56-1.1
p value	0.481^{ns}		0.829^{ns}	

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

The mean pre-injection of UACR was 1294.9±968.26 mg/g in DKD and 13.8±5.99 mg/g in No DKD. The mean post-injection of UACR was 1142.11±1024.06 mg/g in DKD and 13.01±6.87 mg/g in No DKD. The mean difference of UACR was not statistically significant (p>0.05) between pre-injection and post-injection in both groups.

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

UACR (mg/g)	DKD (n=20)		No DKD (n=20)	
	Mean±SD	Range(min-max)	Mean±SD	Range(min-max)
Pre-injection	1294.9±968.26	84.25-3425.9	13.8±5.99	5.12-25.24
Post-injection	1142.11±1024.06	87.26-2427.7	13.01±6.87	5.32-26.35
p value	0.161^{ns}		0.454^{ns}	

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

DISCUSSION

A total of 40 patient with retinopathy are treated with intravitreal injection bevacizumab attending in the department of ophthalmology, Bangabandhu Sheikh Mujib Medical University, Dhaka, during March 2019 to August 2021, were included in this study. Out of which 20 patients having diabetic kidney disease (DKD) and rest 20 patients without diabetic kidney disease (No DKD). Patients considered having DKD if UACR ≥ 30 mg/g or eGFR < 60mL/min/1.73m^2 and No DKD- if UACR < 30 mg/g or eGFR ≥ 60mL/min/1.73m^2. Patients of both sexes and age above 18 years were enrolled in this study. Patient who had intravitreal injection of anti-VEGF any time up until 6 month prior to the study, patient with other ocular disease, patient with end stage renal disease (receiving hemodialysis or eGFR ≤15mL/min/1.73m^2), one eyed patient and pregnant or lactating women were excluded from the study. The present study findings are discussed and compared with previously published relevant studies.

In this present study it was observed that 50.0% patients belonged to age 50-59 years in DKD and 65.0% in No DKD. The age varied from 38-75 years in DKD and from 46-70 years in No DKD group. Kameda *et al.,* (2018) study observed the age variation from 26-81 years, which is consistent with the current study. Similarly, higher age group also observed by O'Neill *et al.,* (2019) and Bagheri *et al.,* (2018) [6 ,4]. The higher mean age and age range obtained by the above authors maybe due to geographical variations, racial, ethnic differences, and genetic causes may have significant influence in their study subjects.

In this current study it was observed that 65.0% patients were male in DKD and 70.0% in No DKD. Male was predominant in both group. Similar observations regarding the male predominant were also observed by O'Neill *et al.,* (2019), Chung *et al.,* (2019), Bagheri *et al.,* (2018) and Hsieh *et al.,* (2018) [6-7, 4, 8]. Ricardo *et al.,* (2019) mentioned in their study that male sex is associated with a more rapid rate of progression and a worse renal outcome in patients with non-diabetic chronic kidney disease (CKD) [9].

Regarding the Serum creatinine status in this present study (Table I) it was observed that the mean pre-injection of serum creatinine level was 1.23±0.53 mg/dl in DKD and 0.87±0.22 mg/dl in No DKD. The mean post-injection of serum creatinine level was 1.19±0.45 mg/dl in DKD and 0.87±0.16 mg/dl in No DKD. The mean difference of serum creatinine level was not significant (p>0.05) between pre-injection and post-injection in both groups. Bagheri *et al.,* (2018) study found the mean serum creatinine was 0.97 ± 0.27 (mg/dl) in baseline and 0.98 ± 0.25 (mg/dl) in 1 month. The mean serum creatinine difference didn't significantly (p>0.05) changed at one month follow-up after receiving the intravitreal injection of bevacizumab, which supports the

present study. Similar observations also observed by Hsieh *et al.*, (2018) and Kameda *et al.*, (2018) [8, 10].

In this present study it was observed that the mean pre-injection of UACR was 1294.9±968.26 mg/g and 13.8±5.99 mg/g in DKD and No DKD respectively. The mean post-injection of UACR was 1142.11±1024.06 mg/g in DKD and 13.01±6.87 mg/g in No DKD. The mean difference of UACR was not statistically significant (p>0.05) between pre-injection and post-injection in both groups. Chung *et al.,* (2020) study observed that the means of UACR before and after IVB injection were higher in patients with diabetes than in control subjects, whereas statistical test revealed no difference between pre- and post-IVB UACR values within patients with diabetes [7]. However, a tendency of worsening albuminuria, that is, residual increase in UACR, was noted with higher baseline UACR, irrespective of whether the patient had diabetes. This suggests that patients with pre-existing renal dysfunction have a relatively higher risk of worsening albuminuria. Although IVB injection is generally safe in absolute change of albuminuria, caution is required in patients with impaired kidney function. O'Neill *et al.,* (2019) study found no significant association between increased intravitreal anti-VEGF exposure and UACR, over an average duration of 31 months [6]. In another study from Chung *et al.,* (2019) showed the mean of UACR both before and after IVB showed no differences between the groups, and the statistical test revealed no difference between pre- and post-IVB UACR values within groups [7]. They found the mean pre-injection UACR was 109.1 mg/g vs. 78.2 mg/g, in DME and no DME respectively. The mean post-injection UACR was 119.4 mg/g in DME and 81.9 mg/g, in no DME. The investigators tried to identify the clinical significance of UACR as a biomarker for DME due to its non-invasive and convenient method of collection from patients, but these results suggest that UACR was not a proper biomarker in DME. Although not statisti¬cally significant, pre-IVB UACR was higher in those with DME, and these patients did not respond as well to IVB. Other studies accomplished that UACR change was not markedly one year after intravitreal injection of VEGF-inhibitors [11-15]. Bagheri *et al.,* (2018) study showed that intravitreal bevacizumab injection was relatively safe in high-risk group of patients. Even though bevacizumab did not increase the mean UACR in their study. The differences in the development of proteinuria following the systemic versus intravitreal administration of bevacizumab might be explained by lower doses used, lower half-life, localized route of injection, and formulations.

CONCLUSION

This study was undertaken to investigate the effect of intravitreal bevacizumab (anti VEGF) injection on renal function. Most of the patients belonged to 6th decade and male predominant in both groups. Intravitreal injection of bevacizumab could not influence renal function among patients with diabetic retinopathy. The present study reinforces the previously revealed effective renal safety profile of intravitreal anti-VEGF in patients with or without DKD.

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