Investigating the safety and effectiveness of concurrent versus consecutive intra-vitreal Ranibizumab injection with phacoemulsification in eyes affected by diabetic macular edema affecting the central region and visually significant cataract

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Aim

Investigating the safety and effectiveness of concurrent versus consecutive intra-vitreal ranibizumab injection with phacoemulsification in eyes affected by diabetic macular edema affecting the central region and visually significant cataract**.**

Methods

A retrospective review was conducted on 80 eyes (41 right) from 80 patients diagnosed with diabetic macular edema affecting the central region and accompanied by visually significant cataract. Data was collected from January 2021 to April 2023. The eyes involved in the study underwent a combined approach involving phacoemulsification and intravitreal injection of ranibizumab or intravitreal injection of ranibizumab followed 3 months later -if the macula was dry- by phacoemulsification (Delayed). Intravitreal ranibizumab injections were repeated (monthly) after phacoemulsification if the macula was not dry. Center-involved diabetic macular edema (Ci-DME) diagnosis and follow up was done by OCT. Follow up extended to 6 months after phacoemulsification.

Results

In the Combined approach, the average age of participants was 60.8 ± 4.5 years, compared to 62.2 ± 4.3 years in the Delayed group ($p = 0.165$). Preoperative and postoperative central foveal thickness were 534.8 ± 103 µ and 266.5 ± 14.9 µ in the Combined group ($p < 0.05$), and 526.5 ± 103 µ and 270.5 ± 18.3 µ in the Delayed group ($p < 0.05$) ($p = 0.2807$). Rebound center-involved diabetic macular edema (Ci-DME) occurred in 29% of the Combined group and 41% of the Delayed group ($p = 0.385$).

Conclusion

Combining phacoemulsification to intravitreal ranibizumab injection in eyes suffering Ci-DME and visually significant cataract is equally effective and safe as performing phacoemulsification after intravitreal ranibizumab injection and resolution of Ci-DME.

Keywords

Cataract; Cataract surgery; Phacoemulsification; Ranibizumab; and Anti-VEGF.

INTRODUCTION

Diabetes Mellitus (DM) affects millions of individuals worldwide with an estimated global prevalence of 6.1 % as of 2021 ((1)) and the effect of DM on the eye are multitude. At the core of eye disease in DM are and diabetic macular edema (DME) and diabetic retinopathy (DR) ((2)). DME involves the buildup of fluid within the retinal layers in the macula and can manifest as either diabetic macular edema affecting the central region (Ci-DME) or diabetic macular edema not involving the central region ((3)).the diagnosis being essentially dependent on retinal imaging, namely optical coherence tomography (OCT) of the macula ((4)). Ci-DME has a significant detrimental effect on visual function ((5)), and the diminution of vision is often aggravated by the concurrent existence of a senile cataract. Cataract extraction surgery by phacoemulsification occasionally induces postoperative macular edema, irrespective of co-morbid DM ((6)). In recent years, the management of DME has undergone significant advancements, with the anti-vascular endothelial growth factor (Anti-VEGF) intravitreal injection agents becoming a widely adopted treatment approach ((2)). With ranibizumab often playing a pivotal role, this study goal is comparing the effectiveness and safety of simultaneous versus sequential intra-vitreal ranibizumab injection and phacoemulsification in the eyes presenting with center-involving diabetic macular edema (Ci-DME) and visually significant cataract, which frequently coexist.

AIM OF THE WORK

Investigating the safety and effectiveness of concurrent versus consecutive intra-vitreal ranibizumab injection with phacoemulsification in eyes affected by

diabetic macular edema affecting the central region and visually significant cataract.

MATERIAL & METHODS

Between January 2021 and April 2023, Ophthalmology Department in Alexandria Main University Hospital conducted a retrospective analysis of 80 patients' eyes (41 right) with diabetic macular edema affecting the central region and visually significant cataract. This retrospective cohort obtained approval from the ethical committee of Alexandria University Faculty of Medicine and complied with the principles set forth in the Declaration of Helsinki. (IRB approval no.: 0306220). The confidentiality of the records was ensured. Patients eligible for inclusion were those diagnosed with type 2 diabetes mellitus (DM), center-involved diabetic macular edema, and a visually significant cataract. Exclusion criteria encompassed patients with severe cataracts that hindered thorough preoperative fundus examination, either through clinical observation or optical coherence tomography. Additionally, individuals who had undergone any intravitreal injections within 6 months prior to the study intervention were excluded, as were those with concurrent ocular conditions such as glaucoma or uveitis. Data obtained from patients' records included demographic information (age, gender), general medical status (type and duration of DM, HbA1c level), preoperative clinical evaluations (including BCVA, converted to LogMAR), anterior segment assessment, intraocular pressure measurement using Goldmann applanation tonometry (GAT), fundus examination via indirect ophthalmoscopy, and various investigative procedures. Surgical procedures performed and postoperative clinical findings and investigations were also recorded. Center-involving macular edema diagnosis was

validated through optical coherence tomography (OCT) imaging (Topcon 2000FA plus, Japan), utilized for central foveal thickness (CFT) measurement. A standard phacoemulsification procedure was performed on the study eyes by an experienced surgeon (MS), with in-the-bag insertion of an acrylic hydrophobic intraocular lens (IOL). Additionally, study eyes received an intravitreal injection of ranibizumab either before the cataract surgery by 3 months after ensuring a dry macula (cataract surgery delayed, Delayed Group) or concurrently with the cataract surgery (Combined Group) (after conclusion of the phacoemulsification procedure), according to the discretion of the surgeon. Postoperative follow up was conducted monthly (clinical and by OCT imaging of the macula) for at least 6 months. The least follow up duration for study inclusion was 6 months after the cataract surgery. Intravitreal injections were repeated monthly until the macula was dry by OCT. The primary end point was the postoperative

RESULTS

This study included 80 (41 right, 51.25%) eyes of 80 patients stratified into group Combined (41 eyes) and Delayed (39 eyes). The demographic features in this cohort study are outlined in Table 1. The mean ± standard deviation of the patients' age was 60.8 ± 4.55 years in the Combined group and 62.21 ± 4.39 years in the Delayed group ($p = 0.1658$). Table 2 shows the preoperative and postoperative clinical characteristics of the study eyes. A statistically analytical improvement was observed in postoperative BCVA ($p < 0.05$, $p < 0.05$) and CFT ($p < 0.05$, $p < 0.05$) compared to preoperative values in both the Combined and Delayed groups, respectively. Furthermore, any

complications were not documented in either cohort. The primary endpoint was achieved in 29 eyes (70.7%) in the Combined group and 23 eyes (59.0%) in the Delayed group (p = 0.385). There were no notable distinctions between the two groups regarding either primary or secondary endpoints.

resolution of the center-involving macular edema. Secondary end points included the postoperative CFT and IOP at the final follow up.

Table (1): Demographic data of the patients

	Combined	**Delayed**	***P* value***
Gender (n)			
Female	21	17	0.6462
Male	20	22	
Age (years)			
Mean±SD	60.8 ± 4.556	62.21 ± 4.396	0.1658
(Min. - Max.)	55 - 67	55 - 67	
Eyes (n)			
OD	19	22	0.4985
OS	22	17	
Type of diabetes			0.8231

Type 1 Type 2	-- 41	--- 39	
Diabetes duration (years) Mean±SD (Min. - Max.)	 28.54 ± 5.577 23 - 38	 28.05 ±5.365 23 - 38	 0.6927
HbA1C Mean±SD (Min. - Max.)	 7.434 ± 0.589 6.8 – 8.5	 7.526 ± 0.605 6.8 – 8.5	 0.4958

Table (2): Postoperative Outcome

	Combined	**Delayed**	***P* value***
Preoperative BCVA (logMAR) Mean±SD (Min. - Max.)	 1.193 ± 0.181 1.0-1.477	 1.175 ± 0.173 1.0-1.477	 0.4911
Postoperative BCVA (logMAR) Mean±SD (Min. - Max.)	 0.3073 ± 0.152 0.0969 -0.5228	 0.3042 ± 0.164 0.0969 -0.5228	 0.9305
Change in BCVA (logMAR) Mean±SD (Min. - Max.)	 0.885 ± 0.247 0.477 – 1.38	 0.871 ± 0.246 0.477 – 1.38	 0.794

Preoperative IOP Mean±SD (Min. - Max.)	 15.73 ± 1.467 14-18	 15.67 ± 1.242 14-18	 0.8308
Postoperative IOP Mean±SD (Min. - Max.)	 15.83 ± 1.548 14-18	 16.03 ± 1.495 14-18	 0.5655
Change in IOP Mean±SD (Min. - Max.)	 -0.09 ± 2.28 -4 – 4	 -0.35 ± 1.81 -4 – 3	 0.572
Preoperative central foveal thickness (microns) Mean±SD (Min. - Max.)	 534.8 ± 103.232 432 - 732	 526.5 ± 103.975 432 - 732	0.7206
Postoperative central foveal thickness (microns) Mean±SD (Min. - Max.)	 266.5 ± 14.952 248 - 295	 270.5 ± 18.32 248 - 295	0.2807
Change in CFT (microns) Mean±SD (Min. - Max.)	 268.3 ± 104.6 137 – 481	 255.9 ± 108.2 137 – 484	 0.603
Number of injections till dryness Mean±SD	 4.098 ± 1.578	 4.026 ± 1.512	0.8357

(Min. - Max.)	2 - 6	2 - 6	
Rebound edema (n, %)			
NO	29 (70.7%)	23 (59.0%)	0.3856
YES	12 (29.3%)	16 (41.0%)	
Complications			
NO	41	39	0.8231
YES	--	--	

DISCUSSION

Intravitreal injection of ranibizumab improves Ci-DME and BCVA for at least 6 months postoperatively, irrespective of the cataract surgery performed simultaneously or sequentially. Studying the demographic characteristics of the study population reveals important insights. There is an almost equal gender distribution in both study groups, reflecting the lack of any gender predilection for the occurrence of either diabetic retinopathy or Ci-DME in this study cohort. This is contrary to other published reports citing slight female predominance therein ((7)). The fact that the age of the study participants was in the sixth decade onwards in both study groups reflects the longer duration of DM in the study patients and hence the propensity to develop DME. This correlation between DM duration and DME development is in agreement with the report by Wang et al ((8)). Another important aspect of diabetic control is the level of glycosylated hemoglobin. Indeed, the fact that it was beyond the normal values in both study groups is in line with the occurrence of DME, as confirmed by other published studies ((9)). The clinical characteristics of the study eyes clearly demonstrate the beneficial effect of both treatment

approaches adopted by the study authors in both study groups. A poor preoperative BCVA clearly demonstrates the combined effect of a visually significant cataract and a Ci-DME in the Combined group and the effect of only the cataract in the Delayed group (phacoemulsification was conducted only after a dry macula was present). The detrimental effect of Ci-DME on visual function is already reported ((5)). The notable enhancement of BCVA in both groups underscores the efficacy of both treatment approaches. The absence of any distinction between the two study groups emphasizes the fact that both procedures were almost equally effective in inducing dryness of the Ci-DME. These findings are further emphasized by the significant improvement of the CFT in both study groups and the lack of a significant intergroup difference as well as y the almost equal number of repeat injections in either group. The fact that the IOP did not change significantly in both study groups and no complications were encountered further emphasize the relative safety of either procedure. Finally, additional evidence of the almost equal efficacy of both procedures is inferred by almost equal success rates in both groups (71% in the Combined and 59% in the Delayed groups), the difference being statistically insignificant.

This study has some limitations. Inclusion criteria for the group Delayed necessitated that only eyes in which the macula became dry after anti-VEGF intravitreal injection were included. This may have introduced a sampling bias since eyes that received intravitreal anti-VEGF and were not dry after 3 months were excluded from the study. However, the study goal is evaluating simultaneous versus delayed phacoemulsification and intravitreal injection of anti-VEGF and not a response of Ci-DME to isolated injection of anti-VEGF. Additionally, the relatively short follow up

duration of 6 months is less informative about the longer term behavior of these eyes after phacoemulsification. Studies with longer follow ups are thus recommended.

In conclusion, combining phacoemulsification to intravitreal ranibizumab injection in eyes suffering Ci-DME is equally effective and safe as performing phacoemulsification after intravitreal ranibizumab injection and resolution of Ci-DME. Given the advantage of a single (combined) procedure over 2 sequential procedures, it is recommended to combine phacoemulsification to intravitreal ranibizumab injection rather than scheduling the 2 procedures separately in eyes suffering Ci-DME and visually significant cataract.

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