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Study of the effect of adding topical Nepafenac 0.1% eye drop on increasing mydriasis in patients with diabetes mellitus type 2

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Abstract: Objective: To evaluate the effect of adding topical Nepafenac 0.1% eye drop on increasing mydriasis in patients with Diabetes Mellitus type 2.

Methods: the study was conducted on 73 eyes of 73 patients who had type 2 diabetes for 5 years or more. The pupil diameter (PD) was measured in the both eyes without dilation using an Autorefractokeratometer (Grand Seiko\GR- 3500 Ka), then the pupils were dilated in the both eyes using topical Tropicamide 1%. A second measurement of (PD) was taken after dilating using the same device. Topical Nepafenac 0.1% were prescribed 3 times a day for 3 days in the right eye. During the review, after 3 days, the pupils were dilated using topical Tropicamide 1%. A third measurement of the (PD) of the both eyes was taken after dilation using the same device. The efficacy of Nepafenac 0.1% was evaluated by determining the increase in (PD) in the eye that received topical Nepafenac 0.1% and comparing it with the other eye that did not receive.

Results: The mean diameter of the pupil in the right eye after dilation was 4.68±0.8 mm and in the left eye was 4.67±0.7 mm (P=0.8). After applying Nepafenac 0.1% topically 3 times a day in the right eye for 3 days, the mean diameter of the pupil in the right eye after dilation was 6.50 ± 0.9 mm and in the left eye 5.10± 0.08 mm (P=0.001). The change in the mean diameter of the pupil in the right eye was 1.82 ± 0.7 mm, and in the left eye was 0.43 ± 0.6 mm.

Conclusion: Topical application of Nepafenac 0.1% showed an increase in pupillary diameter after dilation with Tropicamide 1% in patients with type 2 diabetes mellitus.

Keywords: Non- steroid anti-inflammatory drugs, Nepafenac 0.1%, mydriasis, Tropicamide 1%, Sympathetic innervation, Para Sympathetic innervation.

دراسة فعالية إضافة قطرة النيبافيناك الموضعي 0.1% في زيادة توسع الحدقة لدى مرضى الداء السكري النمط 2

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المستخلص: الهدف: تقييم تأثير إضافة قطرة نيبافيناك0.1% موضعياً على زيادة توسع حدقة العين لدى مرضى داء السكري من النوع 2.

الطرائق: أجريت الدراسة على 73عين لـ73مريضاً مصابين بداء السكري من النمط 2لمدة 5سنوات أو أكثر. تم قياس قطر الحدقة (PD)في كلتا العينين دون توسيع الحدقة باستخدام مقياس أسواء الانكسار الآلي (Grand Seiko \ GR- 3500 Ka)، ثم تم توسيع الحدقتين في كلتا العينين باستخدام Tropicamide 0.1% الموضعي. تم أخذ قياس ثانٍ لـ (PD) بعد التوسيع باستخدام نفس الجهاز. تم وضع نيبافيناك 0.1% الموضعي 3 مرات يوميًا لمدة 3 أيام في العين اليمنى. خلال المراجعة، بعد 3 أيام، تم توسيع حدقة العين باستخدام Tropicamide 1% الموضعي. تم أخذ قياس ثالث لـ (PD) لكلتا العينين بعد التوسيع باستخدام نفس الجهاز. تم تقييم فعالية نيبافيناك0.1% من خلال تحديد الزيادة في(PD) في العين التي تلقت نيبافيناك 0.1% الموضعي ومقارنتها بالعين الأخرى التي لم تتلق النيبافيناك.

النتائج: كان متوسط قطر الحدقة في العين اليمنى بعد التوسيع 0.8±4.68 ملم وفي العين اليسرى كان 0.7±4.67 ملم (P = 0.8). بعد تطبيق نيبافيناك0.1% موضعيًا 3 مرات يوميًا في العين اليمنى لمدة 3 أيام، كان متوسط قطر الحدقة في العين اليمنى بعد التوسيع 0.9±6.50 ملم وفي العين اليسرى 0.08±5.10 ملم (P = 0.001.) كان التغيير في متوسط قطر الحدقة في العين اليمنى 0.7±1.82 ملم، وفي العين اليسرى كانت 0.6±0.43 ملم.

الخلاصة: التطبيق الموضعي للنيبافيناك0.1% أظهر زيادة في قطر الحدقة بعد التوسيع بتروبيكاميد 1% في مرضى السكري من النمط 2.

الكلمات المفتاحية: الأدوية المضادة للالتهاب غير الستيرويدية، نيبافيناك0.1%، توسع حدقة العين، تروبيكاميد1%، التعصيب الودي، التعصيب نظير الودي.

Introduction.

Diabetes mellitus (DM) is considered a global epidemic, and constitutes one of the most important health care challenges [1], as chronic high blood sugar causes damage to multiple organs, especially the eyes, kidneys, nerves, heart and blood vessels [2].

Diabetic retinopathy (DR) is a common complication of diabetes and is still the main cause of blindness in the working age group [3].

Pupillary responses to light stimuli and pupil diameter (PD) are controlled by the Sympathetic innervation (SI) and Para Sympathetic innervation (PSI), which may be affected by Diabetes as a mechanism explaining small PD [4- 5],

In addition, the concentrations of Prostaglandins (PGs) are high in the aqueous humor in diabetic patients [6], and their contraction effect on smooth muscles, including the pupillary sphincter, has been demonstrated in them. Therefore, the PD of diabetic patients is usually smaller than that of healthy people.

Since Diabetic retinopathy (DR) and cataract are more common in these patients, it is very important to provide adequate mydriasis to detect and manage these complications, whether cataract surgery within a good workspace or the diagnosis and treatment of retinal vessel disorders.

Non- steroid anti- inflamatory drugs (NSAIDs) are potent inhibitors of Cyclooxygenase (COX) which play a role in the synthesis of PGs [7]. Nepafenac 0.1% is an ophthalmic NSAID drug that is a potent inhibitor of COX- 1 and COX- 2 for the control of pain and inflammation in ophthalmological practice [8- 9]. In this study, it is assumed that inhibition of prostaglandin synthesis by topical Nepafenac 0.1% increases

the effect of mydriatic drugs such as Tropicamide 1% for example, in patients with type 2 Diabetes Mellitus (DM2).

Research Issue:

Mydriasis is an essential diagnostic and therapeutic procedure in ophthalmic practice. It is necessary for examining the crystal body and detecting pathological changes in it. It also provides a suitable surgical field for cataract extraction in a safe and effective manner. It constitutes an important factor for examining and evaluating pathological changes in the retina and its vessels and in the choroid, and it provides adequate and safe access to retinal and vascular lesions when a treatment procedure such as laser photocoagulation is needed.

In diabetic patients, mydriasis is of great importance as they are more likely to develop cataracts earlier and more frequently than non- diabetics, and diabetic retinopathy as an important cause of jectblindness is treatable in the event of early detection.

This requires providing sufficient pupillary dilation first, and second for examinations for optimal and safer therapeutic intervention.

Subjects and methods

The research sample included 73 patients (32 males, 41 females) of DM2 patients who attended the ophthalmological clinic at Tishreen University Hospital in Lattakia during the period 2021- 2020 and the

The age of the study sample patients ranged from 47 to 69 years, and the average age was 57 years.

The duration of diabetes mellitus ranged from 5 to 14 years, and the average duration was 8 years.

The Inclusion criteria were Type 2 diabetes patients, the duration of the DM2 is 5 years or more, Age between 70- 40 years.

The Exclusion criteria were Type 1 diabetes mellitus, Previous ophthalmic surgery: cataract, posterior vitrectomy, Previous trauma to the eye that damaged the pupillary sphincter or iris, Uveitis/posterior synechiae, Glaucoma / new vascular glaucoma, Iris disorders: Coloboma/ PEX, Taking drugs that block the alpha receptors in the context of prostate diseases, Taking non- steroidal anti-inflammatory drugs systemically or locally within a period of 14 days from the date of the examination, 3rd Nerve pulsy

The (PD) was measured in the both eyes without dilation using an Autorefractokeratometer (Grand Seiko\GR- 3500 Ka), then the pupils were dilated in the both eyes using topical Tropicamide 1% at a rate of 3 times with an interval of 5 minutes and waiting for 15 minutes after the last drop. A second measurement of (PD) was taken after dilating using the same device. Topical Nepafenac 0.1% were

prescribed 3 times a day for 3 days in the right eye. During the review, after 3 days, the pupils were dilated using topical Tropicamide 1%. A third measurement of (PD) of the both eyes was taken after dilation using the same device.

The same observer performed all measurements. Pupil diameter was measured using an Autorefractokeratometer under illumination conditions of the examination room.

methods of the statistics.

Study Design: Comparative Study (Cross Sectional)

1- Descriptive statistics:

Quantitative variables were expressed as mean ± SD.

Qualitative variables were expressed in frequencies and percentages.

2- Inferential Statistical Based on Statistics Laws:

Independent T student test to study the mean differences between two independent groups.

The results are considered statistically significant with a p- value of ＜ 5%.

Adoption of the program IBM SPSS statistics (version20) to calculate the statistical transactions and analysis the results.

Results.

1- Demographic results: there were 32 males (43.80%) and 41 females (56.20%) of DM2 patients. (Figure 1)

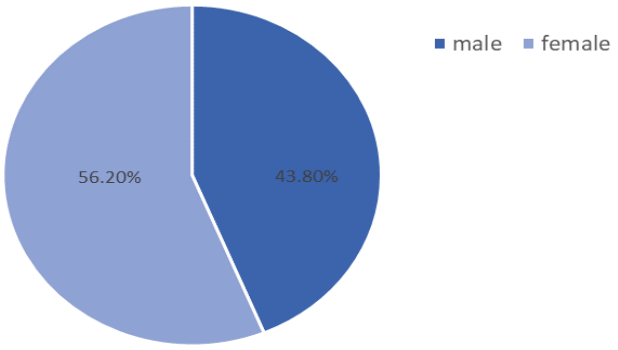

Figure (1) The distribution of the sample between the two sexes.

2- Mean ± SD effects of tested drugs on pupil diameter: PD in the right eye before dilation was 3.19±0.4 mm and in the left eye was 3.17±0.4 mm (P=0.8). after pupil dilation with topical Tropicamide 1%, the mean PD in the right eye was 4.68±0.8 mm and in the left eye was 4.67±0.7 mm (P=0.9).

After applying topical Nepafenac 0.1% the mean PD in the right eye after dilation was 6.50 ± 0.9 mm and in the left eye 5.10± 0.08 mm (P=0.001).

The mean change in PD after dilation before and after applying Nepafenac 0.1% was in the right eye 1.82 mm and in the left eye 0.43 mm (P=0.001). (table 1)

Table (1) Mean ± SD effects of tested drugs on pupil diameter before dilation, after dilation, after dilation and adding Nepafenac, The mean values of the change in PD.

search group	N	OD	OS	P- value
PD before dilation with tropic amide 1%	73	3.19±0.4 mm	3.17±0.4 mm	0.8
PD after dilation with Tropic amide 1% in the	73	4.68±0.8 mm	4.67±0.7 mm	0.9
PD after dilation with Tropic amide 1% and adding Nepafenac 0.1%	73	6.50±0.9 mm	5.10±0.8 mm	0.001
The mean values of the change in PD after dilating with Tropic amide 1% and adding Nepafenac 0.5%	73	1.82 mm	0.43 mm	0.001

N: Number of the sample, PD: Pupil Diameter, OD: Right eye (the study eye), OS: The left eye (the fellow eye), Significant P- Value < 5%.

Discussion.

This study is a cross- sectional comparative study, which evaluated the efficacy of a topical applying of Nepafenac 0.1% in increasing Mydriasis in patients with DM2.

It focused on the criterion of change in pupil diameter after dilation with Tropicamed 1% before and after the applying of Nepafenac 0.1% to evaluate the effectiveness of this drug.

The study included patients with DM2, because diabetic patients are exposed to a greater proportion of inflammatory factors that have the most important role in making the pupil diameter smaller than in non- diabetic patients. Where it was found that high blood sugar level activates the metabolism of arachidonic acid via the COX and lipoxygenase (LOX) pathways and the production of inflammatory mediators such as prostaglandins (PGD, PGE2, PGF2α), thromboxane (TXA2), leukotrienes (LTEL4TC4, LTEL4,LTD4), and it was found that the concentration of these products is high within the aqueous humor and vitreous humor in these patients.

In this study, We found no statistically significant difference in PD between the both eyes before the dilation (P=0.8), we also found no statistically significant difference in PD between the both eyes after dilation(P=0.9), but We found statistically significant difference in PD between the both eyes after dilation before and after applying topical Nepafenac 0.1%, where the mean PD in the right eye that received Nepafenac increased by 1.82 mm (38%), while the mean PD in the left eye that did not received Nepafenac increased by 0.43 mm (9%) (P=0.001).

By comparing the results of our study with international studies, we find that these results are consistent with the findings of Kiziltoprak et al [10] in Turkey,

Zanetti et al [11] in Brazil Cervantes coste et al [12] in Mexico, where these studies confirmed the role of NSAIDs in general and Nepafenac in particular in inhibiting the synthesis of inflammatory factors within the aqueous humor, leading to a decrease their concentration in it and thus reducing their constriction effect on the pupillary sphincter muscle, thus allowing to obtain greater effect of topical mydriatics.

The average diameter of the pupil after dilation and application of Nepafenac 0.1% in the study of Kiziltoprak et al in the study eye was 5.64 mm and in the control eye 5.67 mm, in contrast, the average diameter of the pupil in our study after dilation and application of Nepafenac 0.1% was 6.5 mm and 5.1 mm in the study eye and the control eye respectively.

These differences can be linked to the number of the sample. The number of patients in the study sample of Kiziltoprak et al was 82, of whom only 43 patients had diabetes, compared to 73 patients in our study, all of whom were patients with diabetes.

In our study, 0.1% Nepafenac was administered 3 times a day for 3 days. In the study of Kiziltoprak and colleagues, it was applied 3 times for 1 day before the examination. In the study of Kiziltoprak et al, the pupil was dilated using Cyclopentolate 1% for one time and then measuring the PD after an hour, while in our study, Tropicamed 1% was used for 3 times with an interval of 5 minutes and measuring the diameter of the pupil after 15 minutes.

In Cervantes et al 's study, the measured pupillary diameter at the end of surgery was 7.9 mm in the group receiving Nepafenac, and in our study the largest pupillary diameter after dilation was 7.7 mm. This small difference is due to the exclusion of patients with diabetes in Cervantes et al 's study and their use of a combination of Tropicamed 0.8% and Phenylephrine 5%, while our study included patients with type 2 diabetes and used Tropicamed 1% only. In the study of Cervantes et al, the pupil diameter was measured by a compass from the operating microscope used in cataract surgery, while in our study the pupil diameter was measured by an Autorefractokeratometer under the lighting conditions of the examination room and without surgical intervention.

In the study of Ahmed et al [13], the pupil diameter at the end of the surgical procedure was 7.2 mm, which is lower than the values shown in our study. This is due to the presence of surgical intervention in Ahmed and colleagues' study and manual measurement of the pupil diameter using calipers.

In Zanetti et al 's study, the average diameter of the pupil after dilation was 7.8 mm, which is greater than the values shown in our study. This small difference is due to the exclusion of diabetic patients from the study of Zanetti et al, and the use of a mixture of Tropicamed 0.5% and Phenylephrine 5%, and that their study was conducted on Prednisolone, ketorolac, and Nepafenac.

Conclusion.

The diameter of the pupil in patients with DM2 is affected by the presence of inflammatory factors within the aqueous humor, the diameter of the pupil becomes smaller and its response to topical pharmacological dilators is reduced. The effect of Nepafenac is shown by inhibiting the synthesis of these Factors and nullify their negative effect, so it should be given to patients with diabetes to provide greater dilation of the pupils and facilitate Ophthalmic examinations and interventional procedures.

Recommendations.

1. Giving patients with type 2 diabetes mellitus a drop of Nepafenac 0.1% topicaly 3 times a day for 3 days before conducting ophthalmological examinations and before performing the surgical intervention.
2. Conducting more studies with a larger sample size and other medicinal preparations such as bromfenac and others.

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