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Ameliorative Protective Influence of Etoricoxib Against Chemo Convulsions Correlates with Blood Glucose Levels in Rats

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ABSTRACT

Objective: The effect of Etoricoxib (ETOR) on the link between blood glucose and seizure prevention in chemo-convulsive rats was investigated in this study.

Methods: Pentylenetetrazol (PTZ-105 mg/kg i.p.) at the CD97 dosage was administered to rats to cause seizures. ETOR (10 mg/kg p.o.) was administered for two weeks prior to seizure induction. On the 14th day, the animals were exposed to chemo convulsions, and the efficiency of ETOR in lowering clonus-type chemo convulsions (CC) as well as blood glucose levels were assessed. Morphometric analysis and chimney tests were performed to evaluate ETOR's neurotoxic profile. Actophotometer, rotarod, and hole board tests were employed for behavioral analysis.

Results: When compared to control mice, pretreatment with ETOR (10 mg/kg p.o) resulted in a substantial delay in the onset of CC (P<0.05) and duration of CC (P<0.01). Acute ETOR treatment also considerably lowered blood glucose levels. The chimney test findings show that it has no effect on motor control and is not neurotoxic to the animals.

Conclusion: Behavioral tests also demonstrated that, except for the diazepam-treated groups, no significant changes in muscle coordination, locomotion, or apprehensive behavior were detected in all experimental animals. Finally, the primary findings of this study showed that the PTZ group had considerably greater levels of hyperglycemia, which is reflected in the rat's early onset and longer duration of chemo-convulsions. However, ETOR medication reduced high blood glucose levels as well as the onset and duration of seizures, indicating ETOR's impact on blood glucose reduction and the relationship between blood glucose and seizure responses.

Keywords: Blood glucose, Chemo convulsions, Etoricoxib, Pentylenetetrazol, Seizure protection

INTRODUCTION

The significance of glucose proportion in the human body has been described in both *in vivo* and *in vitro* research, indicating that threshold glucose proportion is required to enable synaptic transmission.[1] However, circumstances such as hyperglycemia increase brain injury causing ischemia and hyper excitability in the neuronal environment. Hyperglycemia is a condition characterized by abnormally high blood sugar or glucose levels. It happens when the body doesn't make or use enough insulin, a hormone that converts glucose into energy in the cells.[2,3,4] Hyperglycemia is a common diabetes complication that can affect both diabetic and non-diabetics. Both Hyperglycemia and hypoglycemia can cause seizures if left untreated. According to known research, lowering extracellular glucose levels may reduce seizure activity by decreasing neuronal excitability.[5]

Seizures have been noticed in various central nervous system (CNS) disorders, and they have been linked to proinflammatory processes that cause CNS illness. Alternatively, metabolic abnormalities such as hyperglycemia and hypoglycemia can cause CNS damage, resulting in seizures; seizures in endocrine illnesses can be caused by autoimmune, metabolic, and neuroinflammation.[6,7] Inflammations are mostly caused by Cyclooxygenases. Cyclooxygenases are myeloperoxidases that mediates the conversion of arachidonic acid to PGH2, which is then converted to physiologically active end products like PGD2, PGE2, PGF2, PGI2, or thromboxane A2 (TXA2) via specific synthases.[8,9] COX-1 and COX-2 are two isoforms of cyclooxygenase. COX-1 is a housekeeping enzyme, whereas COX-2 is a fast-inducible

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inflammation-related enzyme. According to gene expression data, COX-2 was the dominant isoform in human pancreatic islets under baseline conditions.[10]

According to the data, the main and important endogenous prostanoid produced by COX-1 and COX-2 is PGE2. In a pancreatic cell line called HIT cells as well as in humans, PGE2 reduced glucose-induced insulin production.[11-13] As a result, inhibiting COX-1 or COX-2 lowers PGE2 levels, which improves insulin secretion. A recent *in vitro* study, found that using a selective COX-2 inhibitor called celecoxib, a pancreas-cell line called INS-1E cells released more glucose-stimulated insulin.[14] However, the *in vivo* effects of selective COX-1 or COX-2 inhibition on insulin secretion remain poorly understood and need to be clarified through additional research. Hence, this investigation was decided to establish the impact of ETOR an inhibitor of COX-2 on the correlation between blood glucose and seizure prevention in chemo convulsive rats, which was induced by toxic chemicals such as pentylenetetrazol (PTZ 105 mg/kg i.p) to the experimental animals.

METHODS

Drugs and Chemicals

The drugs etoricoxib, diazepam, and pentylenetetrazol were obtained from Yarrow chem. Pvt LTD, India, and dissolved in appropriate solvents. The dose of ETOR (10 mg/kg b.w) and diazepam has been used successfully in similar experimental models and the dose of ETC based on suggested human treatment regimes has been used successfully to closely replicate human scenarios of use.[15,16] Etoricoxib was suspended in 0.25% carboxymethyl cellulose, diazepam in 1% w/v gum acacia, and for PTZ normal saline is used. All chemicals that were purchased were analytical grade.

Animals and Ethical Approvals

Albino adult male rats with weight ranges between 160-175 g were chosen and housed in conventional laboratory-housing settings such as 23°C, humidity of 55%, and light-dark cycles. Many basic science studies of diabetic complications have concentrated on STZ-induced diabetes using exclusively male mice, despite the fact that diabetes is known to affect both sexes in patients and in some genetic animal models. Therefore, we have chosen exclusively male animals for our study.[17] All animals were given access to food and water ad libitum throughout the experiment. The experimental protocols were duly approved (SVCP/IAEC/II-10/19-20) by the IAEC (Institutional Animal Ethics Committee) in accordance with the recommendations of the Committee for Control and Supervision on Animal Experiments (CPCSEA), New Delhi, India. To avoid bias, randomized methods of allocation of animals were followed with respect to treatments as different experimental groups.[18]

Experimental Design

Induction of Chemo Convulsion

A total of 24 rats were randomly divided into four groups of six animals each (n=6) according to the following acute study design duration of 14 days. Group I was served as control and treated with normal saline (2ml/kg of NS 0.9%) whereas Non-Diabetic Hyperglycemia (Group II) received 20% glucose solution through intraperitoneally 30 minutes before administration of PTZ. Non-diabetic hyperglycemia is known as impaired glucose regulation, is defined as elevated blood glucose levels that are not in the diabetic range. Group III and Group IV animals received diazepam and standard ETOR, respectively, along with 20% glucose before the induction of chemo convulsions. To check the correlation between glucose levels and seizure protection, rats were given 20% glucose solution (to reduce drug-induced hypoglycemia mortality of animals) except control animals.[19-21]

PTZ was administered at a dose of 105 mg/kg i.p at its CD97 convulsive dose to induce chemo convulsions on 14th day. After administration, animals were kept separately in transparent cages (25 × 15 × 10 cm) to better observation of the occurrence of a clonus type of convulsion about the next 30 min.[22,23]

Group I - Control (NS-2ml/kg.p.o)

Group II- NDH (Glucose -20%) + PTZ (105 mg/kg i.p)

Group III - NDH (Glucose -20%) +DIAZ (2mg/kg.i.p) + PTZ (105 mg/kg i.p)

Group IV - NDH (Glucose -20%) +ETOR (10 mg/kg.p.o) + PTZ (105 mg/kg i.p)

Morphometric Analysis

The body weight of all experimental animals was carefully documented at regular intervals to examine the effect of acute ETOR administration on experimental animals.

Measurement of Blood Glucose Concentrations

Glucose measurement was performed in all experimental groups immediately before and after the seizure tests. To evaluate blood glucose concentration, a little drop of blood (10 µL) was collected from the tip of the rat's tail and placed on a test stripe (glucose oxidase/peroxidase reactive strips) of Dr. Morepen one touch glucometer. The

glucose-level reading appeared and was observed in 5 seconds. The glucose tolerance was measured hourly for three hours.

Acute Neurotoxicity Test

The neurotoxic profile of ETOR was evaluated using a chimney test. This test is considered as one of the gold standard tests to check the neurotoxic profile of ETOR. Rats were kept in a horizontal cylindrical tube with a diameter of 3cm and a length of 25cm. The capacity to exit the tube backward in a specified time limit (1 minute) has been calculated as a criterion for neurotoxicity.[24]

Behavioral Parameters Analysis

During the investigation, the animals were also observed for any behavioral changes. An activity cage was used to track the locomotor activity. Rats were kept one by one in the activity cage and the overall activity count was reflected as locomotion was noted until the cutoff period. The increased count was taken as stimulant activity in the central nervous system, whereas decreased count was regarded as depressing activity.[25]

The head dip test was used to assess the animals' exploratory behavior. Individually, they were kept on the hole-board apparatus till the cut-off period. During a three-minute period, the total number of head pocking was noted.[26-28]

The rotarod is one of the most extensively used experimental tools for evaluating the test drug's muscle grip strength and muscle coordination.[29-31] The rota-rod system supplied by Inco Instruments', Ambala, India, was used to automatically record the latency to fall animals from the revolving bar, which rotates at a speed of 25 rpm. To avoid experimental bias, all animals received sufficient trials.

Statistical Analysis

Results were expressed as mean ± S.E.M. The significance of the difference between the treatment group and control was determined by one-way ANOVA followed by Tukey's Multiple Comparison Test. Graph Pad Prism 5.0 Version (Graph Pad Software, Inc., San Diego, California, USA) was used to conduct the statistical analysis. The significance level was set at $P<.05$.

RESULTS

The Measurement of Blood Glucose

Blood glucose concentrations were assessed in all experimental groups hourly for three hours before and after the seizure induction by PTZ (Table 1). The results of the blood glucose levels before seizure induction show that all of the experimental animals' blood glucose levels were normal, with no deviations observed in any group. Except in the control groups, there was an increase in glucose levels after the induction of chemo convulsions preceded by glucose ingestion. However, the results indicated that a significant reduction of blood levels (at 1hr $^{*}P<.05$, at 2h** $P<.01$) was observed in ETOR-administered animals compared with NDH + PTZ groups. Similarly, blood glucose elevations were significantly reduced by the DIAZ groups also observed.

Table 1. Effect of ETOR on blood glucose level on chemo convulsive rats

Groups	Changes in blood glucose level (mg/dL)			
	Basal Values Before seizure induction	After seizure induction		
		1 h	2 h	3 h
CONTROL	97.70 ± 3.50	96.60 ± 1.24	94.40 ± 2.06	95.89 ± 1.74
NDH + PTZ	109.70 ± 2.40	135.50 ± 2.05	127.10 ± 5.71	131.00 ± 2.80
DIAZ + PTZ	111.50 ± 2.87	121.80 ±4.04^{***,a}	109.10 ± 1.18^{*,b}	107.20 ±1.75^{*,c}
NDH +ETOR + PTZ	107.80 ± 1.93	120.12 ±3.56^{***,a}	106.50 ± 1.60^{*,b}	113.140 ± 3.70^{*,b}

The number of animals (n=6): Values are mean ± SEM: One-way ANOVA was used to analyze the data, followed by Tukey's Multiple Comparison Test.$^{*}P<.05$, $^{**}P<.01$ & $^{***}P<.001$ when compared to control groups.$^{a}P<.05$,$^{b}P<.01$ & $^{c}P<.001$ compared to NDH+PTZ groups. ns: Non-Significant. The significance level was set at $P<.05$. **NDH:** Non-Diabetic Hyperglycemia; **DIAZ:** Diazepam; **ETOR:** Etoricoxib; **PTZ:** pentylenetetrazol

PTZ Induced Chemo Convulsions

In the PTZ model, the onset of clonus convulsion (Figure 1) and its duration (Figure 2) were observed and calculated in all experimental animals. Results of the study indicate that pretreatment with ETOR (10 mg/kg p.o) showed a marked delay in the onset of CC ($^{*}P<.05$) followed by a marked reduction of the duration of CC ($^{**}P<.01$) compared with control animals. From the results, it is evident that pretreatment with ETOR showed a protective effect ($P<.05$) upon the duration of the clonic seizure form in rats, along with the delay of onset of clonic seizures.

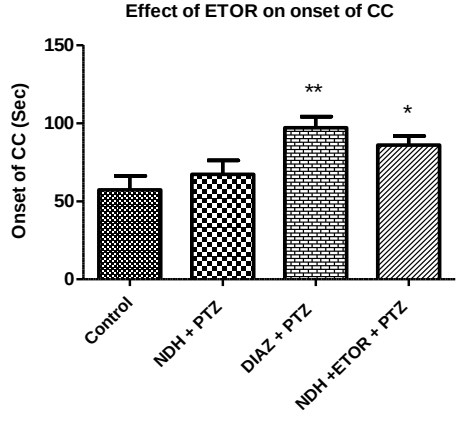

Figure 1. The effect of ETOR on the onset of CC

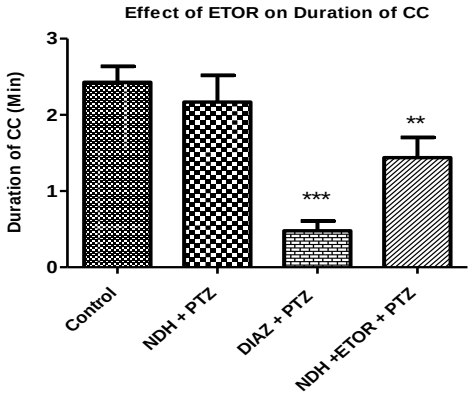

Figure 2. The effect of ETOR on duration of CC

The effect of ETOR on PTZ-induced chemo convulsions is depicted in Figures 1 and 2.According to the results, pretreatment with ETOR (10 mg/kg p.o) showed significant protection chemo convulsions caused by PTZ, which is evident by the delay of onset followed by a significant reduction of the duration of CC. Values are mean ± SEM; **P*<.05, ** *P*<.01 & *** *P*<.001 when compared to control groups; ns: Non-significant. The number of animals (n=6).

Morphometric Analysis

To demonstrate the effect of ETOR treatment, a morphometric examination of all experimental animals was performed, and the results are displayed in Table 2. Throughout the study period, the body weight of the experimental animals was monitored at weekly intervals. According to the findings, ETOR treatment resulted in significant changes in body weight, with a particularly noticeable increase in NDH groups treated with ETOR (164.30 ± 4.07, *P*<.05) on day 14 compared to control (145.70 ± 5.01) and NDH + PTZ NDH + PTZ (155.20 ± 5.47) treated groups. As a result, morphometric research revealed that ETOR has a favorable effect on body weight gain, which demonstrates the absence of harmful effects (Figure 3).

Table 2. Effect of ETOR on body weight of experimental animals

Groups	Changes in body weight(g)		
	Day 1	Day 7	Day 14
CONTROL	135.90 ± 3.16	142.40 ± 3.59	145.70 ± 5.01
NDH + PTZ	139.10 ± 3.47 ^{ns}	142.30 ± 2.73 ^{ns}	155.20 ± 5.47 ^{ns}
DIAZ + PTZ	136.70 ± 3.13 ^{ns}	141.50 ± 2.45 ^{ns}	151.50 ± 2.81 ^{ns}
NDH +ETOR + PTZ	140.43 ± 2.62 ^{ns}	145.20 ± 4.37^{ns}	164.30 ± 4.07*

NDH: Non-Diabetic Hyperglycemia; **DIAZ:** Diazepam; **ETOR:** Etoricoxib; **PTZ:** pentylenetetrazol **; Statistical comparison**: Values are mean ± SEM; **P*<.05,** *P*<.01, and *** *P*<.001 compared to the control group, NS: Non-significant. The number of animals (n=6).

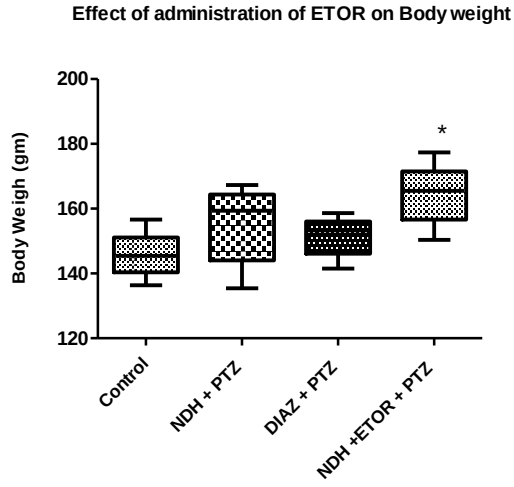

Figure 3. The effect of administration of ETOR on body weight

Figure 3. shows the effect of ETOR on experimental animals' body weight on day 14. Values are mean ± SEM; **P*<.05,** *P*<.01, and *** *P*<.001 compared to the control group, NS: Non-significant. The number of animals (n=6).

Acute Neurotoxicity Test

A conventional chimney test with rats was used to explore ETOR's neurotoxic characteristics. According to the findings, all experimental rats given ETOR at 10 mg/kg i.p. could evacuate the tube within the one-minute time limit by climbing back up as soon as they reached the other end, suggesting that ETOR has no effect on motor control and is not neurotoxic (Figure 4).

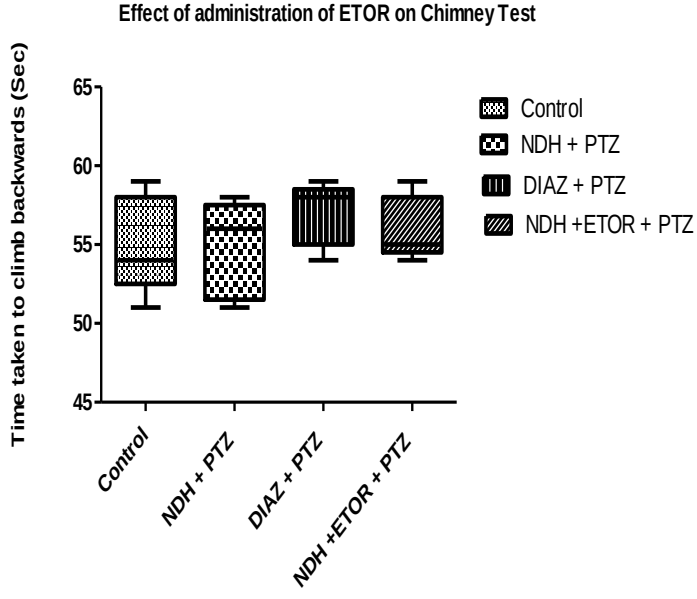

Figure 4. The effect of administration of ETOR on Chimney Test

Figure 4. shows the results of the chimney test, which demonstrated that all of the experimental animals could climb backwards out of the tube within a stipulated time (1 minute), indicating that ETOR has no effect on motor control and is not neurotoxic to the animals. Values are mean ± SEM; **P*<.05,** *P*<.01, and *** *P*<.001 compared to the control group, NS: Non-significant. The number of animals (n=6).

Behavioral Parameters Analysis

Figure 5(a) shows the effect of ETOR on the muscle grip strength of chemo convulsive rats in the rotarod test. The effects of ETOR on locomotion and the head tip test are depicted in Figures 5(b) and 5(c), respectively. In the rota rod test, animals treated with NDH+ PTZ and NDH + ETOR + PTZ showed no significant differences in muscle grip strength compared to control groups. However, diazepam-treated groups showed a steady decrease in muscular grip strength, confirming the conventional drug's relaxing characteristics. The locomotion results showed that, except the standard diazepam received ($^{*}P<.05$) group, the remaining experimental groups, such as NDH+ PTZ and NDH + ETOR + PTZ, showed no significant differences in locomotion compared to control groups. Similarly, no changes were observed in the head dip test except diazepam received groups (** $P<.01$). The results of behavioral tests revealed that all experimental animals, with the exception of diazepam-treated groups, showed no significant changes in muscular coordination, locomotion, or anxious behavior and the results were similar to those of control animals.

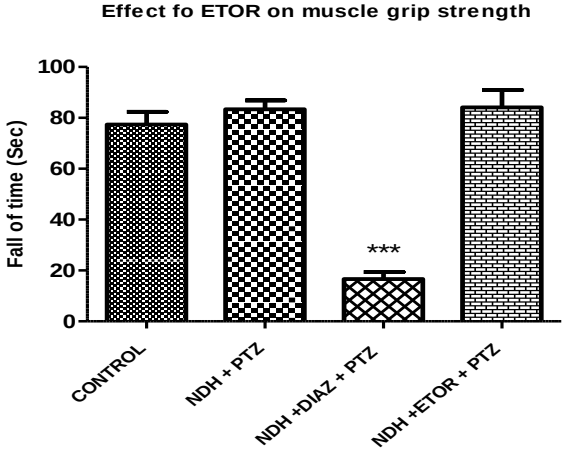

Figure 5a. The effect of ETOR on muscle grip strength

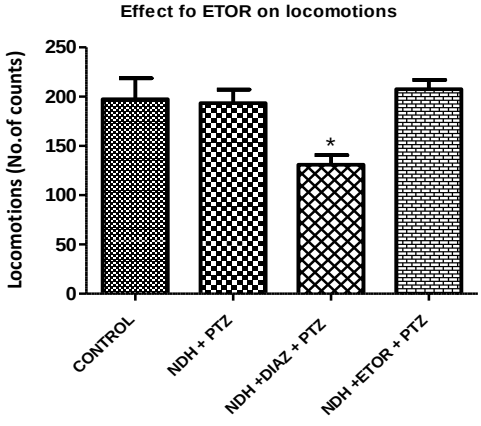

Figure 5b. The effect of ETOR on locomotion

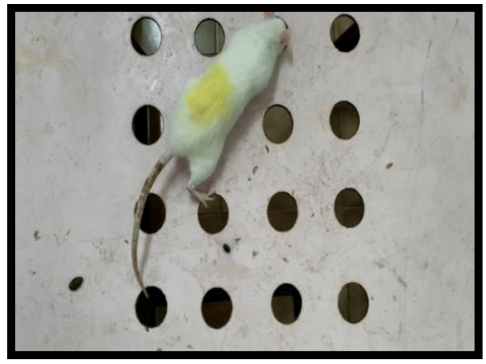

Figure 5c. Head tip test

Figure 5. Behavioral analysis: Muscle coordination, Locomotion and Head tip test. Values are mean ± SEM; *$P<.05$,** $P<.01$, and *** $P<.001$ compared to the control group, NS: Non-significant. The number of animals (n=6).

DISCUSSION

Metabolic diseases are predicted to cause widespread neurological impairments, including seizures. Experimental studies (both *in vivo* and *in vitro)* indicate that a certain level of glucose concentration is vital to enable synaptic transmission. But in rat models, elevated glucose is proconvulsant and has been linked to neuronal over activity followed by cerebral hypoxia-induced brain damage, whereas fasting-induced hypoglycemia protects against this neurotoxicity.[32,33] Hence, this investigation is designed to expound the correlation between blood glucose and seizure-provoking responses in experimental groups. The results of this study also reflect the results of earlier studies, which indicated that there was a massive rise of blood glucose in NDH groups when compared control groups. But the acute administration of ETOR showed significant reduction of blood levels at 1hr ($^{*}P<.05$), at 2h ($^{**}P<.01$) compared with NDH+ PTZ groups.

According to available reports, neuronal cell excitability owing to hyper stimulation may be affected by both hypoglycemia and hyperglycemia that leads to a short circuit of the brain that may cause seizures when left untreated.[34,35]

According to data about 25% of diabetics suffer from seizures.[36-41] In this investigation, to correlate the association between blood glucose and seizures, onset of clonus convulsion and its duration were observed and calculated in all experimental animals. From the results, it is evident that pretreatment with ETOR showed a protective effect ($P<.05$) upon the significant reduction in the duration of the clonic seizure (**$P<.01$), a delay of the onset of ($^{*}P<.05$) clonic seizures (Figure 3) along with the

significant reduction of blood glucose levels compared to control animals.

Alternatively, results from morphometric analysis show that ETOR administration caused a significant rise in body weight with a particularly notable increase were observed in NDH groups treated with ETOR (164.30 ± 4.07, $P<.05$) on day 14 compared to control (145.70 ± 5.01) and NDH + PTZ NDH + PTZ (155.20 ± 5.47) treated groups. Additionally, the results from conventional chimney test demonstrating that ETOR has no effect on motor control because all animals were all able to leave the tube backwards within a specified time limit, which indicates ETOR has no neurotoxic effects. Results of the behavioral test suggested that no significant changes were observed in muscle coordination, locomotion's and anxiety behavior of all experimental animals except diazepam-treated groups. However, a gradual decrease in muscle grip strength was observed in diazepam-treated groups, confirming the standard drug's relaxing properties. The results were comparable with control animals.

Overall, ETOR administration significantly lowered the glycemic control as well as the incidence and duration of seizures to a beneficial extent compared to control groups. As a result, the findings reveal that seizure duration is linked to blood glucose levels, implying that seizure duration is prolonged in NDH + PTZ animals. So, the findings of our study also reflect and confirm the findings of previous studies that found a link between hyperglycemia and prolonged seizure duration.[42-44]

CONCLUSION

The primary findings of this study revealed that the NDH + PTZ groups had significantly higher glycemic levels, which is reflected in the rat's early onset and longer duration of chemo-convulsions. As a result, the findings show that seizure duration is linked to blood glucose levels, implying that seizure duration is longer in the NDH + PTZ groups. Treatment with ETOR, on the other hand, significantly reduced elevated blood glucose levels as well as the onset and duration of seizures in rats, suggesting the link between blood glucose and seizure responses. In conclusion, the findings of this study suggest that ETOR has a beneficial effect on blood glucose-level reduction and seizure protection in PTZ-induced chemo convulsive rats.

Ethics Committee Approval: The experimental protocols were duly approved (SVCP/IAEC/II-10/19-20) by the IAEC-SVCP (Institutional Animal Ethics Committee of SVCP) in accordance with the recommendations of the Committee for Control and Supervision on Animal Experiments (CPCSEA), New Delhi, India. To avoid bias, randomized methods of allocation of animals were followed with respect to treatments as different experimental groups
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Author Contributions: Concept – J.R.; Design – J.R.; Supervision – C.A.; Data Collection and/or Processing – N.N.P.; Analysis and/or Interpretation – R.P.; Literature Search – S.A.; Writing Manuscript – J.R.; Critical Review – N.K.S., D.P.P.
Conflict of Interest: The authors have no conflicts of interest to declare.
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