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Original Research Article

Comparing the antiepileptic effects of atorvastatin, celecoxib, ashwagandha, clove oil, and Sodium valproate on chemo-shock induced seizures in male Wistar albino rats

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ABSTRACT

Background: Antiepileptic potential of statins, COX inhibitors and other herbal medications are to be evaluated in experimental animals so that the most efficacious can be translated for human use as an adjunct to the commonly used anti-epileptic drugs.
Methods: This experimental animal study grouped 30 male Wistar albino rats into 6 groups with each containing 5 rats of which one group was control, one was the standard drug and the other 4 were treatment groups which received Atorvastatin, Celecoxib, Ashwagandha and Clove oil. These drugs were administered 30 minutes prior to administering Pentylene-tetrazole which induced convulsions and the various seizure parameters were analysed. The blood samples of the animals were also assessed for anti-oxidant activity by measuring superoxide dismutase and catalase levels in the blood.
Results: The onset of seizure was significantly delayed by Ashwagandha (2.55±0.94), similar to the latency shown by the standard drug (2.09±1.21). The duration of convulsions was very significantly reduced in all the 5 drug groups in comparison to the control ($p<0.001$). The clonic jerk duration was not reduced as effectively as the standard drug. The duration of recovery time amongst the various groups was also significant ($p<0.05$). The SOD and Catalase levels of no groups showed any possible association between the anti-epileptic efficacy of these drugs and the anti-oxidant enzyme levels.
Conclusions: Ashwagandha has good anti-epileptic efficacy not less than the standard drug when the various drug groups were compared.

Keywords: Epilepsy, Anti-epileptic drugs, Atorvastatin, Celecoxib, Ashwagandha, Clove oil, Sodium valproate

INTRODUCTION

Epilepsy is known to be the most common multifaceted chronic neurological disease worldwide and is also one of the ancient medical diseases recorded. In the olden days, epilepsy was thought of as a condition that portrays an evil mental state or possession, whereas, some cultures considered epileptics as people with supernatural powers, and it was also thought to be transmissible.[1,2] Seizures

were always considered to be a divine malady and a mystery. Hippocrates was the first to demythologize epilepsy and identify the association between seizures and disorder in brain function.[2] An epilepsy is defined as "a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures."[3] It is marked by repeated and unprovoked seizures. Epilepsy affects around 50 million people worldwide.[4] The antiepileptic drug armamentarium boasts of a myriad of drugs from varied chemical classes, yet the effective control and cure of epilepsy is still elusive. Modern medicine has advanced profoundly over all these years, and sizeable progress has been made in the pharmacological management of epilepsy with the introduction of novel anti-epileptics in recent times but the mechanism of epilepsy on the cellular basis still continues to be a mystery and we are yet to comprehend the exact pathophysiology behind the origin of seizures. This hinders our ability to find an effective treatment modality for seizures.

The current approaches to anti-epileptic therapy are usually directed at the control or suppression of seizures and thereby keep the patient seizure free without affecting their normal brain function. These drugs are selected based mainly on their efficacy, safety and tolerability for specific type of seizures.[5]. And yet one third of epileptic patients continue to present with refractory seizures. Even in patients in whom the pharmacotherapy is found to be effective, the current AEDs have no role in stopping the progression, completely curing the patient off the disease or modifying the underlying natural history of the disease. Furthermore, the existing AEDs are also associated with a number of adverse effects, teratogenicity and other long-term toxicities. All these factors thereby substantiate the need to develop new and more effective anti-epileptic drugs.

Exploring the anti-epileptic potential of drugs that are otherwise used for various alternative indications can also be utilized in the epilepsy research. Researches has found that developing various strategies in stopping the inflammatory response that develops in the brain after an initial epileptogenic injury is one of the possible targets of epilepsy-prevention.[6] Noticeable increase in the expression of the key inflammatory mediators in the brain is seen after seizures which can lead to secondary damage in the brain and increase the chances of repetitive seizure[7]. Strategies that intent to bring down the inflammatory cytokine and other mediator levels can prove to be milestone in the antiepileptogenic therapy.[6] Hence, efforts that are expended in investigating the antiepileptic or neuroprotective potential of COX inhibitors and statins, which reduce the inflammatory cytokines, can prove to be a revolutionary step in the discovery of adjuncts to AEDs and provide a helping hand to the patients.

Likewise, usage of herbal medicines for the treatment of epilepsy is an age-old medical practice amongst many cultures. Various herbal extracts can be used as antiepileptic remedies. Around 60 different herbs mentioned in Ayurveda literature have been studied for their antiepileptic activity.[8] Herbal plants like Ashwagandha and clove oil are drugs that improve the brain and nervous system function. These drugs enhance the resilience of the body to stress and helps to improve the cell-mediated immunity and thereby increases the body's defence against diseases. Traditional herbal medicines as well as anti-inflammatory drugs which can produce potential anti-epileptic effects can therefore be evaluated in animal models and if found effective can be effectively utilised as adjunct therapy in patients' who are refractory to drugs and in those with high seizure frequency. These drugs are also likely to have fewer adverse effects as compared to the standard AEDs, which also proves to be a potential benefit for the patient. Hence, in our study, the investigators sought to explore the activities of potential anti-epileptic effects of the drugs, atorvastatin, celecoxib, ashwagandha and clove oil and comparing it with the standard anti-epileptic drug, sodium valproate by making use of Pentylenetetrazol induced seizures in male albino rats.

METHODS

This study was an experimental animal study conducted by the department of pharmacology, Amrita Institute of Medical Sciences, Kochi in collaboration with Central Animal House, AIMS, Kochi. The study was conducted from March 2022 to June 2022. 30 healthy adult male Albino rats, weighing 200-500g were used for this study. The animals were not kept fasting before the test and the food and water was provided ad libitum. The experiment was designed and conducted according to animal ethics guidelines.

The rats were grouped into 6 with 5 animals in each. The same group was not used more than once. The test was performed on 6 different days. On a single day, only one group of animals were taken for the study following which they were rehabilitated. Group 1 (Standard Control group): Animals were served standard diet, Group 2 (Atorvastatin group): Animals were given Atorvastatin (7.5 mg/kg) intra peritoneally, Group 3 (Celecoxib group): Animals were given Celecoxib at a dose of 40 mg/kg intra peritoneally, Group 4 (Sodium valproate): Animals were given Sodium valproate 300 mg/kg intra peritoneally, Group 5 (Ashwagandha group): The powder was made into a purified form using Soxhlation.[9] Animals were provided with Ashwagandha 300 mg/kg intra peritoneally, Group 6 (Clove oil group): Animals were given extract of Clove oil 0.1 ml/kg intra peritoneally. On any single day, the animals were weighed in the beginning and the test drug was administered in the appropriate dosage. 30 minutes after the administration of the test drug, Inj. Pentylenetetrazol was administered at a dose of 60 mg/kg intraperitoneally to induce seizures and the animal was observed for the convulsions for 30 minutes and the seizure parameters of each animal is noted. The same method is repeated for all the 5 animals of the respective group taken on a single day.

The seizure parameters that were analysed includes: latency of seizure onset, duration of convulsions, duration of clonic jerks, duration of recovery time and number of seizure episodes. After observing the animal for 30 minutes following the administration of Inj. Pentylenetetrazol, the animals were anaesthetized by keeping them in an anaesthesia chamber which contained 3% Isoflurane for not less than 1 minute for collecting the blood samples which were collected from lateral tail vein of the animal. The blood samples, after coagulation was then centrifuged for 20 minutes at 2000-3000 rpm to obtain the serum and was then stored at -20° C and were later evaluated for catalase and superoxide dismutase levels using ELISA kits. The time taken for each of the seizure parameters with each of the five test drugs were then compared and analysed.

RESULTS

On comparing the latency of seizure onset, it was noted that, Ashwagandha showed the maximum efficacy by delaying the onset of seizure by a mean 2.55 minutes, which was in fact more than what the standard AED sodium valproate produced (2.088 min) although it was statistically not significant. However, the latency produced by Ashwagandha was significant when compared with that produced by Atorvastatin ($p<0.05$) (Figure 1).

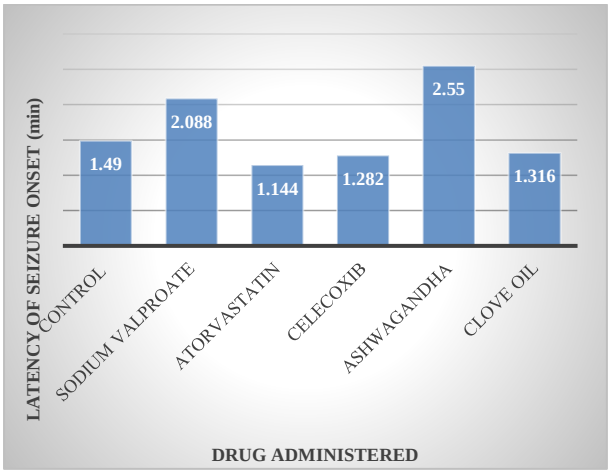

Figure 1: Bar diagram comparing the mean time taken for seizure onset among the various drug groups.

The other drugs did not show comparable efficacy in prolonging the time for seizure onset. When duration of convulsions was compared among the various groups, it was seen that all the drug groups produced significant reduction in duration of seizures in comparison with the control animals and the Ashwagandha group was protected in a very highly significant manner ($p<0.001$) (Table 1). Ashwagandha was almost as efficacious as the standard AED in reducing the duration of seizures with the mean duration of convulsions lasting 0.416 minutes with that in the standard drug group being 0.388 minutes. Next to Ashwagandha, Celecoxib was the other drug to effectively reduce the seizure duration (1.18 min). Clove oil produced convulsions for a mean duration of 1.848 minutes while a mean 2.43 minutes of seizure occurred in the Atorvastatin group. However, none of the drugs produced statistically significant reduction in comparison to the standard drug.

Table 1: Showing comparison of duration of convulsion among the various drug groups with respect to the control group and the standard drug group.

Comparison of duration of convulsions		P value
Control	Standard drug	<0.001
	Atorvastatin	0.015
	Celecoxib	0.001
	Ashwagandha	<0.001
	Clove Oil	0.005
Standard drug	Control	<0.001
	Atorvastatin	1.000
	Celecoxib	1.000
	Ashwagandha	1.000
	Clove oil	1.000

The recovery time was the other parameter that was analysed. This denotes the time the animal remained free from seizure. In terms of the recovery time, Valproate and Ashwagandha were equally efficacious and produced significant anti-epileptic efficacy in comparison to the control. The animals of the valproate group remained seizure free for a mean 26.30 minutes while those which received Ashwagandha for 24.83 minutes (Table 2).

Table 2: Showing comparison of duration of recovery time among the various drug groups.

Group	N	Mean	SD	P value
Control	5	13.32	8.33	0.008
Sodium Valproate	5	26.30	1.48	
Atorvastatin	5	16.48	6.73	
Celecoxib	5	20.54	8.28	
Ashwagandha	5	24.83	1.30	
Clove oil	5	23.42	1.76	

Clove oil provided an effective recovery time of 23.42 minutes and the group that received celecoxib remained seizure free for a mean 20-minute duration.

Atorvastatin did not show much anti-epileptic efficacy when the recovery time was taken into consideration. The antioxidant status assessed by measuring SOD and Catalase showed that, the highest concentration of mean SOD and Catalase levels were seen within the control group of animals. The mean concentration of SOD was the highest in the Control group (0.580 ng/ml) and lowest within the Valproate (0.276) and Ashwagandha group (0.260) (Figure 2).

The Catalase levels also reduced within the groups that received AED and were highest in the control groups

(Figure 3). These findings demonstrate that there was no significant improvement in the anti-oxidant levels when an AED is given. Hence it can be construed that AEDs have different mechanistic ways in controlling the initiation and propagation and halting of the seizures.

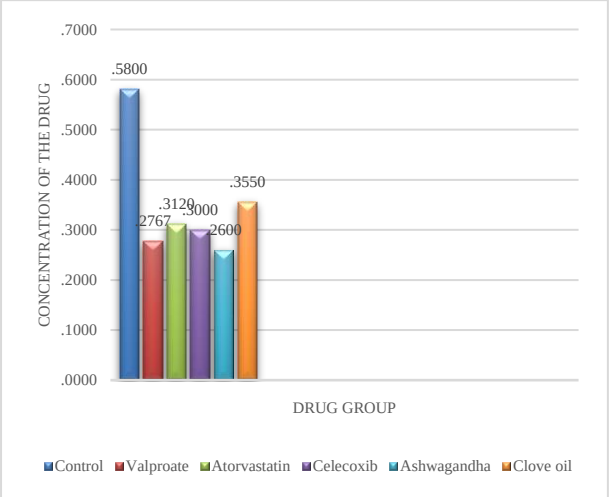

Figure 2: The mean concentration of SOD concentrations among the various drug groups.

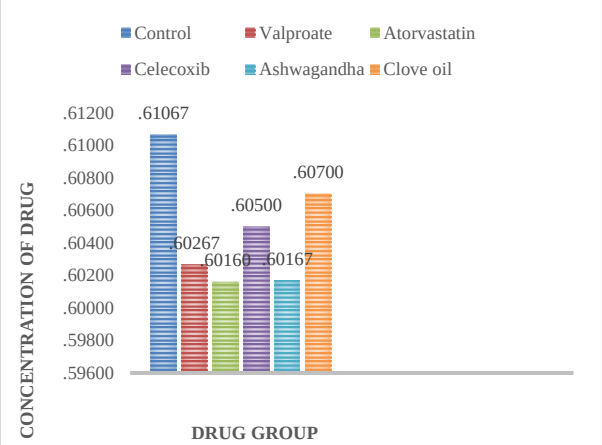

Figure 3: The mean concentration of catalase concentrations among the various drug groups.

DISCUSSION

Our study mainly aimed at investigating 2 major factors; the anti-epileptic potentials of 4 drugs, namely, atorvastatin, celecoxib, ashwagandha and clove oil and compared them with the standard anti-epileptic drug – sodium valproate and the role of antioxidants in the antiepileptic action of these drugs. The animals used were male Wistar albino rats with a mean weight of 170.5 grams. The negative control group were administered Normal saline while the positive control groups received sodium valproate at a dose of 300 mg/kg which is a standard AED. The various drugs showed significant anti-epileptic activity when compared to the negative control group, but, determining the individual anti-epileptic efficacies and comparing the relative activities was the aim of our study. Atorvastatin, an HMG-COA reductase inhibitor, is used in the treatment of hyperlipidaemic states. In addition to this, it is also known to possess neuroprotective and anti-excitotoxic effects in various cerebral pathophysiologies.[10] On analysing the various seizure parameters, Atorvastatin did not show equivalent anti-epileptic effect as the standard drug. However, when the duration of convulsions was compared with that of control, the anti-epileptic potential was found to be significant ($p<0.05$) (Table 1). This was consistent with a study by Singh A et al in which the administration of Atorvastatin produced a significant reduction in the duration of seizures[11] .A study by Koshnoud et al. which assessed the anti-convulsant activity of Atorvastatin in mice by comparing the latency to onset of Straub tail and tonic-clonic seizures and protection from hind limb tonic extension and death, showed that Atorvastatin produced potent anticonvulsant property when given in a dose dependant manner.[12] Cyclooxygenase-2 (COX-2) is an enzyme that is found to be expressed in the brain following an inflammatory or neurodegenerative process.[13] Studies have shown that inflammatory mediators like COX-2 are rapidly induced in the brain during seizures and this increased expression can lead to secondary damage to the brain and further increase the likelihood of repeated seizures.[7] Nadeem et al in his study to evaluate the anti-epileptic effect of Celecoxib by observing the parameters of onset of tonic hind limb extension (THLE), duration of THLE and of clonic jerks, noticed that Celecoxib reduced the duration of clonic seizures and also delayed it significantly [14].In our study, the animals that received Celecoxib at a dose of 40 mg/kg, took a mean time of 1.28 minutes for seizure onset [Vide figure 1] and the duration of convulsion period was 1.18 minutes which was significantly less when compared to the control group (7.08 min) (Table 1). Ashwagandha (Withania somnifera) is a commonly used herb in the Ayurvedic medicine system. Ashwagandha also called Indian ginseng is a popularly used home remedy for many ailments. Apart from this, it is also proven to have various immunomodulatory, anti-inflammatory and antianxiety properties.[15,16] Raju et al in his study showed that when given at a dose of 300 mg/kg, Ashwagandha greatly reduced the mean duration of hindlimb tonic flexion and extension, clonus, and stupor, and there was no postictal depression in PTZ induced seizure models.[15] In our study, Ashwagandha extract given at a dose of 300 mg/kg produced marked anti-epileptic action. The mean latency of seizure onset was 2.55 min, which was in fact greater than the latency of Valproate (2.088 min), but however was not statistically significant (Figure 1). The mean duration for which the rats developed convulsions was only a mere 0.41 min which is significantly reduced when compared to the NS pre-treated control group (7.086 min) (Table 1). Out of the five animals in the group that received the 300 mg/kg dose of Ashwagandha, one animal was completely protected from developing tonic-clonic convulsions, but however had a clonic jerk for 30 seconds. The mean duration of clonic jerks for the entire group was

2.03 minutes. The animals remained in the recovery state for majority of the time (24.83 min) similar to the standard drug group (26.30 min) which reveals the potential anti-convulsant property of Ashwagandha (Table 2). Clove oil is also a medicinal herb that finds its effect in a wide variety of traditional medicinal practices. Eugenol, which is the major component of clove oil, is shown to have potential anti-convulsant and anti-stress properties in a few studies.[17] Clove oil has been shown to delay the onset of seizure in a study by Avanthi et al when given in a dose of 0.075 ml/kg and a statistically significant delay in onset of seizure was seen for a dose of 0.1 ml/kg.[18] In our study, the animals of the group which received 0.1 ml/kg of clove oil, it was seen that the mean latency of seizure onset was 1.31 minutes (Figure 1). The mean duration of convulsions was 1.85 minutes which was significant in comparison to the control animals (7.08 min) (Table 1). Clonic jerks were present for a mean duration of 3.42 minutes and the mean recovery time with clove oil was 23.40 minutes which is comparable with the standard drug group (26.29 min) (Table 2). Oxidative stress has a major role in the initiation and progression of a seizure. Oxidative stress is caused due to an imbalance between the production and accumulation of reactive oxygen species (ROS) within the cells[19.] Herbal medicines have a lot of antioxidants and could have a probable role in mitigating seizures. The presence of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), guaiacol peroxidase (POX), Peroxiredoxins (Prxs) and various other enzymes indicate anti-oxidant property. In our study, due to financial constraints, we have limited the estimation of anti-oxidant enzymes to 2, namely Superoxide dismutase (SOD) and Catalase. This was to determine for any relation of these anti-oxidants in seizure control and impact of the AEDs on these enzymes. SOD belong to a group of metalloenzymes that plays a major role in reactive oxygen species mediated injury.[20] They play a major role in the defense against oxidative stress in the body. SOD helps in the conversion of superoxide anion free radical (O_2^-) into molecular oxygen and hydrogen peroxide (H_2O_2).[21] SOD also provides anti-inflammatory action and helps to prevent the pre-cancerous changes in cells.[22] Catalase is another major antioxidant enzyme present within the peroxisomes in majority of organisms. Catalase with the help of a two-step reaction helps in the breakdown of hydrogen peroxide molecules into oxygen and water.[23,24]

The antioxidant status assessed by measuring SOD and Catalase showed that, the highest concentration of mean SOD and Catalase levels were seen within the control group of animals. The mean concentration of SOD was the highest in the Control group (0.580 ng/ml) and lowest within the Valproate (0.276) and Ashwagandha group (0.260) (Figure 2). On evaluating the relation between the SOD concentration and seizure profile, it is seen that an indirect correlation exists between the two, i.e., the drugs which produced the highest anti-epileptic action showed the lowest SOD concentration while those with the minimal action showed highest concentration of SOD. This was consistent with the findings of the study by Shehta et al.[25] The Catalase levels also reduced within the groups that received AED and were highest in the control groups (Figure 3). These findings demonstrate that there was no significant improvement in the anti-oxidant levels when an AED is given. Hence it can be construed that AEDs have different mechanistic ways in controlling the initiation and propagation and halting of the seizures. Seizures can develop from various pathological processes. The drugs we evaluated produced anti-epileptic actions by various methods. The aim was to determine if these drugs produced the action by reducing the oxidative stress as it has a great role to play in the pathogenesis of epilepsy. However, from our findings, it was evident that, the drugs that were evaluated sodium valproate, atorvastatin, celecoxib, ashwagandha and clove oil played no role in protecting the animals from oxidative stress and produced anti-epileptic action from a different mechanistic action other than anti-oxidant effect.

Limitations

All the negative aspects of an animal study, being the one lowest in the hierarchy, is a limitation to our study as well. We have only used comparison of 4 drugs from an existing panel of drugs and polyherbal formulations that has potential anti-epileptic effect. We have not characterised the individual principle that is producing the anti-epileptic effect from ashwagandha and clove oil. Anti-oxidant determination was minimal due to fund and time constraints.

CONCLUSION

It was observed from current study that treatment with these drugs were beneficial in epilepsy although these are not as effective as the standard anti-epileptic drugs. Our study concluded that among the 4 drugs studied, the most efficacious in providing anti-epileptic action was Ashwagandha which was non-inferior to sodium valproate. Furthermore, it was also concluded from the SOD and catalase levels that none of these drugs helped in reducing the oxidative stress and therefore have a different mechanistic action other than producing anti-oxidant effect.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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