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Early Stage Clinical Trial of Ginger (*Zingiber officinale*) as an Add-on Antiepileptic Therapy in Children with Generalized Epilepsies

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Abstract

Epilepsy is a disorder of the brain characterized by the generation of epileptic seizures. Botanicals and herbal materials including some parts from plants are prepared and taken in many ways for treatment of children ill with epilepsy. Conventional antiepileptic drugs are associated with adverse effects on long term therapy. Based on the promising preclinical biological tests exhibited by ginger, the early stage clinical trial was conducted in children with generalized epilepsies as prospective hospital based randomized controlled study, in whichginger was taken by volunteers as an adjunct therapy. Study revealed that participants who administered add-on ginger plus AEDs as carbamazepine and sodium valproate were increasingly seizure free during 6 months therapy to reach 93 and 80% respectively. while all of them experienced reduction in seizure duration and seizure frequency. Significant reduction in side effects (urination, defecation, salivation, vomiting and heart burn) produced by AEDs and/ or by seizure was observed. Moreover, it was also worth noted that all patients tolerated ginger very well and no signs of toxicity or serious side effects were reported. In conclusion, ginger could has a high potential in treatment of epilepsy, especially if further studies are conducted to explore its possible anticonvulsant effect alone and/or as co-drug in combination with AEDs

Key words: Ginger, Epilepsy,Add-on antiepileptic, Clinical trials.

Introduction

Epilepsy is a group of neurological disorders characterized by epileptic seizures [*1-3]. Epilepsy* is one of the most common neurological disorders after stroke and affects at least 50 million people worldwide [4]. During the past 20 years, major clinical and research efforts have sought to characterize the status of health related quality of life in epilepsy [5].Childhood epilepsies beginning in the first few years of life are frequently characterized by seizures that are resistant to available treatments, including antiepileptic drugs [6].The goal of management of children with epilepsy is to enable the child and his family to lead a life as free as possible of the medical and psychosocial complications of epilepsy. This comprehensive care needs to go beyond simply trying to control seizures with minimal adverse drug reactions. Other factors including social, psychological, behavioral, educational, and cultural dimensions affect children with epilepsy, their families and their

close social networks [7].

Nature is a rich source of biological and chemical diversity. The unique and complex structures of natural products cannot be obtained easily by chemical synthesis. A number of plants in the world have been used in traditional medicine remedies [8-13].

Botanical products including ginger extracts have been found to block seizures in animal models as well as their centuries old traditions of use in treatment of seizures with actions that include effects on Gama amino butyric acid(GABA) receptors and voltage-gated ion channels, anti-inflammatory and neuroprotective effects [14]. The twenty century has witnessed considerable progress in anticonvulsant drug development [15]. However, phytomedicines can potentially play an important role in the development of new antiepileptic drugs to pharmacoresistent patients [16]. Ginger, the Rhizome of Zingiber officinale, is one of the most widely used species of the family (Zingiberaceae) and is a common condiment for various foods and beverages. Ginger has a long history of medicinal use dating back 2,500 years in China and India [17]. It was proved that ginger is used as anti-epileptic and ant seizures [14], anti-inflammatory, analgesic and anti-pyretic [18, 19], gastro protective [20], cholesterol lowering and hypoglycemic [21, 22], antibacterial and antiplatelet [23. 24], cardio protective [25], radio protective, anticancer [26-28], antiemetic [29, 30].

Materials and Methods

A randomized, cross over controlled study was conducted. Only patients with partial epilepsy were recruited. Treatment was continued for twenty four weeks.

Type of Study

This prospective hospital-based randomized cross over controlled study investigated add-on ginger effect on different types of primary generalized epilepsies in children aged 2-16 years. Adequate methods of concealment as well as randomized trials were considered.

Ginger Rhizomes Supplement

Ginger was offered to each volunteer in the form of crude powder mixed with teaspoonful of jam.

Types of participants

The participants in this study were children with diagnosed primary generalized epilepsies aged 2-16 years. Patients identified from a clinical database and Electroencephalogram (EEG) records attended Wad Medani Children Teaching Hospital Referred Clinics. Data recorded prospectively on demographics and clinical information, seizure types, antiepileptic drug treatment details, seizures onset frequency, AEDs side effects and remission rates. Epilepsy diagnosis was made for each patient, based on the clinical and EEG features according to the ILAE classification where possible. Only children with primary generalized seizures including patients with typical absence seizure (petit mal), atypical absence seizure, generalized tonic-clonic seizure, atonic seizure and myoclonic seizure were included.

Types of interventions

Study groups

Patients with primary generalized epilepsies aged 2-16 years on monotherapeutic drugs of either Sodium valproate(n=15) or Carbamazepine(n=15) drugs were included as control groups. While another two test groups received either sodium valproate plus ginger (n=15) or carbamazepine plus ginger(n=15) were considered. The whole sample size was sixty children. Ginger in test groups was administered orally in daily dose of 250, 500 and 1000mg for 2-5, 6-11 and 12-16 years old children respectively, mixed with teaspoonful of jam extemporaneously for six months. Children in all groups were followed and assessed every month.

Outcome measures

Complete cessation of seizure, reduction in

seizure frequency, reduction in seizure duration and presence or absence of side effects induced by AEDs and/or seizure.

Ethical approval

Ethical clearance was obtained from the ethical committee, University of Gezira and Ministry of Health.Verbal and written consent were obtained from each child´s parent accepted to be included in the study.

Statistical analysis

This was done by using SPSS version 14.0 (SPSS Inc. Chicago, IL.USA).All values were expressed as mean ± SD. Data were analyzed by one-way ANOVA and difference between means was assessed by a two-tailed Student's T-test. $P \leq 0.05$ was considered statistically significant

Results:

An early-stage clinical trial of the antiepileptic effects of ginger used concomitantly (Add- on) with AEDs, as carbamazepine and sodium valproate in children generalized epilepsies. Titration of findings made as case by case basis according to the clinical responses and observational data collected from patients and/ or parents, compared to the base- line data.

As shown in Table I patients (n= 15) treated with carbamazepine drug alone experienced seizure free in 87% of participants while patients (n=15) treated with add-on ginger showed seizure free in 93% of participants. In Table 2 patients (n=15) treated with sodium valproate drug plus ginger experienced seizure free in 80% while those treated with sodium valproate alone (n=15) experienced seizure free in 73%. All of patients experienced reduction in seizure duration and frequency with insignificant differences ($P \leq 0.244$) compared to the control. Children treated with AEDs plus add- on ginger experienced significant ($P \leq 0.05$) reduction in side effects produced by the AEDs and/ or by seizure, mainly urination(7/7= 100%), vomiting (15/15= 100%) and heart burn (6/ 6=100%) and to less extent defecation (1/2= 50%), salivation(9/13=69%) compared to those administered AEDs alone. Moreover, it was also worth noted that all patients tolerated ginger very well and no signs of toxicity or serious side effects were reported.

Discussion

Challenges associated with herbal medicines must be overcome before conducting clinical trials [31].For that herbal therapies and as the case of the traditional safety use of kitchen-herb-ginger and its promising activity in animal epilepsy models provide reasonable basis for the early-stage clinical study [14,32.33], such therapies have the potential to yield new treatments and preventive options of epilepsy. They could also have novel mode of action, leading to find new molecular targets [34].

Few clinical studies have been conducted using natural traditional nonconventional anti epileptic drugs in man and to less extent in children. One of which was the use of water extract of *Nigella sativa* in patients with their usual medication whereas, three adult patients out of 12 were seizure free by four weeks [35]. Another clinical trial using cannabidiol- enriched cannabis was conducted by Porter and Jacobson [34] whereas, only two (11%) out of 19 reported complete seizure freedom. Sixteen (84%) of parents reported a reduction in seizure frequency and six (32%) reported a 25- 60% seizure reduction.

In this study, the *In-vivo* trail of ginger on children with generalized epilepsies proved that it can be used as co-drug in treatment of generalized epilepsies and to counteract the effects produced by AEDs and/ or seizure.

Conclusion

The present investigation of ginger used concomitantly with AEDs, mainly carbamazepine and sodium valproate in childhood generalized epilepsies, appears to be of encouraging results and prove that ginger could has a place in epilepsy treatment since no side effects were observed as

to require ginger intake discontinuation. The improvement of seizure burden that obtained, the positive satisfactory parents/patients reports and the absence of the negative side effects commonly associated with AEDs and/ or seizure provide evidence of promising effects.The overall positive results on seizure control in test groups of patients with generalized childhood epilepsies suggest and recommend that further studies of ginger are warranted.

Table 1: Children with generalized epilepsies and became seizure free during six months of treatment with carbamazepine (250-500mg/ kg/day) and/ or with add-on ginger(250-1000mg/kg/day)

Time	Treatments	
	Patients received Carbamazepine alone	Patients received Carbamazepine plus Ginger
One month of treatment	0/15(0%)	2/15(13%)
Two months of treatment	1/15(7%)	8/15(27%)
Three months of treatment	1/15 (7%)	11/15(85%)
Six months of treatment	13/15(87%)	14/15(93%)

Table 2: Children with generalized epilepsies and became seizure free during six months of treatment with sodium valproate (250-500mg/ kg/day) and/ or with add- on ginger (250-1000mg/ kg/day)

Time	Treatments	
	Patients received Carbamazepine alone	Patients received Carbamazepine plus Ginger
One month of treatment	0/15(0%)	2/15(13%)
Two months of treatment	1/15(7%)	8/15(27%)
Three months of treatment	1/15 (7%)	11/15(85%)
Six months of treatment	13/15(87%)	14/15(93%)

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