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Efficacy of a traditional herbal formula against drug-resistant childhood epilepsy

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In about one-quarter of childhood epilepsies, there is no complete response to the routine, available antiepileptic drugs (AEDs). In traditional Persian medicine (TPM), *Paeonia lactiflora* and *Anacyclus pyrethrum* have been known for their anticonvulsant effects. The aim of this study was to evaluate the therapeutic efficacy of a combined herbal formula consisting of the dried root of *P. lactiflora* and *A. pyrethrum* in childhood drug-resistant epilepsy (DRE). This single-arm before/after clinical trial was conducted on 46 children with DRE. The patients were observed for three months before as well as thirteen weeks after the administration of this traditional herbal preparation at a dose of 15 mg/kg/day. The frequency and duration of seizures were evaluated using the Hague seizure severity scale (HASS). There was a statistically significant reduction in both the frequency and duration of seizures after treatment with the herbal preparation (p-values were <0.001 and <0.05, respectively). A statistically significant response to the herbal formula started after eight weeks of treatment. The traditional formula of *P. lactiflora* and *A. pyrethrum* could be considered as a complementary medicine for treating childhood DRE. However, further studies are needed to provide more evidence of its benefits and possible harms and also determine the precise mechanisms of action of this formula as a medicinal remedy for epilepsy.

Keywords: *Anacyclus pyrethrum*, Child, Drug-resistant epilepsy, *Paeonia lactiflora*, Traditional medicine

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Epilepsy is one of the most common neurological diseases[1,2]. Approximately a quarter of children with epilepsy show varying degrees of drug resistance called "intractable" or "refractory" epilepsy. Drug-resistant epilepsy (DRE) has been defined as a persistent seizure activity despite adequate trials of at least two tolerated and appropriately chosen antiepileptic drugs (AEDs)[3]. DRE affects all aspects of a child's development, leading to significant impairment in quality of life, as well as behavioral and psychiatric problems, including depression, sleep and mood disorders, cognitive delay, and poor scholastic performance[4]. Moreover, some patients experience unacceptable AED-related side effects, such as teratogenicity, liver toxicity, gastrointestinal complications, etc[5]. In general, drug resistance and interactions, high costs, and AED-related side effects are the main challenges in drug administration, particularly in children[6].

Therefore, the need for complementary therapies with fewer side effects is evident. Traditional Persian medicine (TPM), which is based on thousands of years of experience, has provided effective therapies in this regard[7-9]. A combined herbal formula of the dried roots of *Paeonia lactiflora* Pall. and *Anacyclus pyrethrum* DC., has been used for the treatment of epilepsy in TPM[10-12]. Although numerous studies have evaluated the antiepileptic properties of various plant components, few studies have evaluated the efficacy of these herbal remedies in clinical trials. The aim of the current study was to evaluate the efficacy of the

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traditional preparation of *P. lactiflora* and *A. pyrethrum* in the treatment of childhood DRE.

Methodology

The present study was conducted in the pediatric ward of Ghaem Hospital (Mashhad, Iran). This study was designed as a single-arm before/after clinical trial and was in accordance with the Declaration of Helsinki (1989 revision)[13]. The study protocol was reviewed, approved, and monitored by the research and ethics committee of Mashhad University of Medical Sciences (license number: Ir.mums.res.1392.911259161) and was registered in the Iranian Registry of Clinical Trials (no. IRCT2015091515790N2).

Materials and Methods

Participants

Parents of all the patients signed the informed consent form to participate in the trial. Inclusion criteria for the participants enrolled in this study were as follows: Patients aged 4 to 15 years with DRE (two to five AEDs at the time of inclusion), occurrence of at least one epileptic seizure during the four-week baseline period, and constant antiepileptic treatment at least one month before the study. Exclusion criteria were pseudo-seizures, neurodegenerative diseases, chronic diseases (such as diabetes mellitus, thyroid dysfunction, and liver or kidney diseases). Patients whose parents had sufficient literacy skills to complete the questionnaire were selected for the study. The brain imaging studies and the electroencephalography (EEG) records were analyzed by a pediatric neurologist and the seizure types were determined.

Preparation of the traditional product

The dried roots of *P. lactiflora* and *A. pyrethrum* were purchased from a local herbal store in Kerman, Iran and were authenticated by a pharmacognosist. The plant parts were washed to remove debris and then air-dried (25°C). Afterwards, the herbal materials were pulverized, passed through an 80-mesh sieve, and kept at 4°C. Combined herbal materials were prepared for encapsulation in 250-mg capsules with the ratio recommended in TPM (Table 1). Quality control of the preparation was performed according to the World Health Organization (WHO) guidelines[14].

Intervention

Eligible patients were carefully monitored for 3 months and then, depending on their body weight, their parents were asked to give them one to three capsules per day after meals (15 mg/kg) for 13 weeks. AED treatment, with at least two but not more than five drugs, was continued and no other AEDs were added to or withdrawn from their regimens within one month before the study.

Outcome measures and safety assessment

The severity of seizures was set as the primary outcome measure. The parents were asked to complete the questions on the Hague seizure severity scale (HASS) at home. HASS is a parent-completed scale to quantify seizure severity[15]. The patients were examined weekly by a pediatric neurologist, and based on the frequency and the duration of the recorded seizures, the response to treatment was graded as “seizure-free”, “good response” (50–99% reduction), “poor response” (1-49% reduction), and “no response”. Secondary outcomes included safety measures. Laboratory assessments including the liver function test (LFT) and complete blood count (CBC) were performed before and after the study. Parents of the patients were asked to report any side effects of the intervention. The herbal preparation was immediately discontinued in cases with an increase in the duration or the frequency of seizures. The child patients were hospitalized if they had any serious manifestations, and others were followed up in an outpatient clinic.

Statistical methods

All the data were analyzed using Statistical Package for the Social Sciences software (SPSS), version 23 (SPSS Inc., Chicago, IL, USA). $p\text{-value}<0.05$ was considered statistically significant. The assumption of a normal distribution in the data was examined with the Kolmogorov–Smirnov test. The Friedman test was conducted to evaluate the difference in the frequency and duration of seizures during 13 weeks. The Kruskal–Wallis analysis was performed to compare the seizure variables in different seizure types. Fisher's exact test was used to evaluate the relationships between gender and seizure type with the duration and frequency of seizures.

Table 1 — Components of the herbal formulation

Plant	Part used	Possible active constituents	Quantity per capsule
P. lactiflora Pall.	Root	Penta-galloyl glucose Paeoniflorin Albiflorin	125 mg
A. pyrethrum DC.	Root	Not specified	125 mg

Results

Pharmaceutical characterization

The Folin-Ciocalteu method was used to determine total phenolic contents in terms of gallic acid equivalent (GAE) in mg/g of the drug. Based on the equation of the calibration curve ($y = 0.007x + 0.006$, $R^2 = 0.999$), the capsules were standardized according to total phenolic content (GAE mg/250 mg capsule) and were equivalent to 6.5±0.5 gallic acid per 250 mg capsule.

Enrollment of the participants

A total of 85 patients were assessed for eligibility, 46 of which were enrolled in the study. A detailed description of the patients' enrollment and analysis is presented in Figure 1.

Baseline characteristics

In the present study, 44 patients completed the treatment period, 30 (68%) of which were boys and the rest (32%) were girls. Two patients were withdrawn during the treatment period. About 46% of the patients had focal impaired awareness seizures, 39% had generalized seizures, 9% had focal aware seizures, and 6% had unknown onset seizures. Two children had two different types of seizures (generalized and focal aware seizures). In 29.5% of the patients, there was a positive family history of epilepsy. The clinical features and demographic data of the patients according to the type of seizure are presented in Table 2. There was a significant difference in the daily attack duration between different types of seizures at the beginning of the study (p-value<0.05). The most common concomitantly used AEDs in this study were carbamazepine and phenobarbital and the most frequent psychotropic AEDs were benzodiazepines. Other AEDs were sodium valproate, lamotrigine, vigabatrin, and phenytoin.

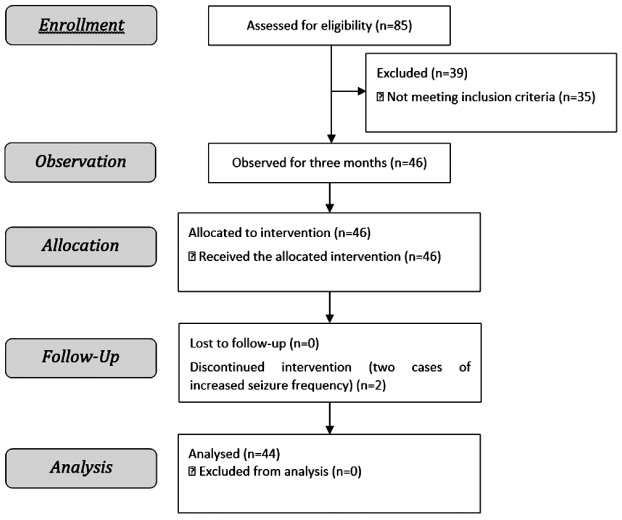

Fig. 1 — TREND flowchart of the study.

Clinical response

After 13 weeks of intervention, there was a significant difference in both the frequency and the duration of seizures (p-values were <0.001 and <0.05, respectively). A significant improvement was specially observed after 8 weeks of treatment with the traditional preparation (Fig. 2 and Fig. 3). Subgroup analysis of the seizure type demonstrated that there was no significant relationship between the type of seizures and the response to the traditional preparation in term of frequency and duration during 13 weeks of treatment (p-value = 0.42 and 0.33, respectively).

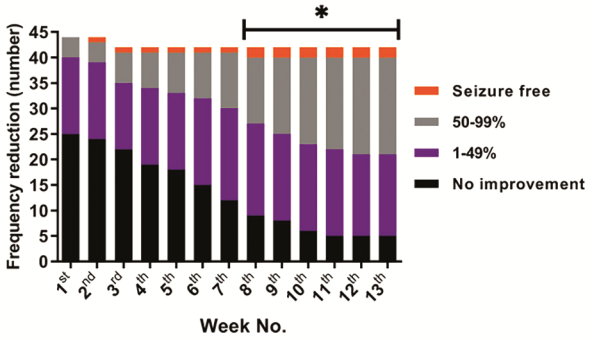

Fig. 2 — The mean frequency of seizures in the study group. * Statistically significant compared to the same week before the treatment (p-value<0.05).

Table 2 — Baseline characteristics of the patients according to the type of seizure

Variables	Focal impaired awareness (Mean ± SD)	Generalized (Mean ± SD)	Focal aware (Mean ± SD)	Unknown onset (Mean ± SD)	p-value*
Age (month)	107.05±8.08	86.81±10.57	90.01±19.96	112.11±22.27	0.21
Age of onset (month)	24.55±6.62	12.56±4.59	19.33±7.35	4.67±1.86	0.30
Disease duration (year)	6.37±0.60	6.06±0.94	5.67±1.56	7.83±2.77	0.72
Number of attacks (per day)	4.47±6.90	7.44±7.97	27.40±41.14	3.33±3.21	0.056
Duration of attacks (seconds per day)	146.00±64.27	21.79±8.95	22.67±18.67	18.01±11.14	0.006

*Kruskal–Wallis analysis

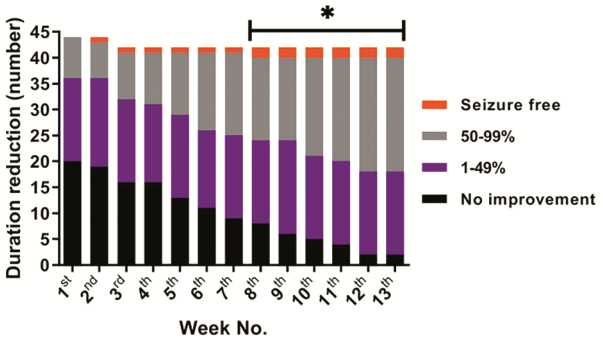

Fig. 3 — The mean duration of seizures in the study group.* Statistically significant compared to the same week before the treatment (p-value<0.05).

Moreover, there was no significant relationship between gender and response to the treatment in terms of the frequency and duration of seizures (p-value = 0.1 and 0.3, respectively).

The traditional preparation was relatively well tolerated by the participants. CBC and LFT were normal before and after the study and no serious adverse effects were reported. However, two patients with focal aware seizure reported an increase in the frequency of seizures in the second and third weeks of the intervention and were excluded from the study. One patient reported a headache and aggressive behavior; seven patients experienced increased sleep duration; and two patients demonstrated restlessness.

Discussion

In this study, the efficacy of a traditional preparation of *Paeonia lactiflora* L. and *Anacyclus pyrethrum* L. was studied in various types of drug-resistant childhood epilepsies. The results showed that the frequency and the duration of seizures were improved during 13 weeks of intervention and a significant response was observed after the 8th week. Two children suffering from focal aware seizures experienced an increase in the frequency of seizures. This increase might not be merely due to the administered traditional formula, since various other factors such as the nutrition status and even different types of seizures may be responsible for this increase[16,17].

This is the first study to investigate the efficacy of the combination of *P. lactiflora* and *A. pyrethrum* in treatment of children with DRE. Previous studies have demonstrated the therapeutic potential of *P. lactiflora* and *A. pyrethrum* in animal models.

Anacyclus pyrethrum DC., which belongs to the Asteraceae family, is commonly known as "Akarkara" in TPM. This plant has immunostimulating, anticonvulsant, antidepressant, antioxidant, and memory-enhancing activities[18]. Several studies have shown the efficacy of *A. pyrethrum* in the treatment of epilepsy. Manouze et al. indicated that the aqueous and methanolic extracts of *A. pyrethrum* root have anticonvulsive and neuroprotective effects on kainic acid-induced status epilepticus in mice[19].

In similar studies, administration of the hydroalcoholic extract of *A. pyrethrum* significantly prevented seizure-induced oxidative stress and cognitive impairment in rats[20,21].

Maximal electroshock (MES)- and pentylenetetrazole (PTZ)-induced seizure models are the most commonly used preliminary screening tests for determining the anticonvulsant potential of drugs. The MES-induced model is a characteristic model for assessing generalized tonic-clonic seizures, whereas the PTZ-induced model is considered an absence seizure model[22,23]. The possible antiepileptic mechanism of *A. pyrethrum* in the PTZ-induced model was proposed to be mediated by enhancing GABAergic neurotransmission[24]. According to Pahuja et al., the anticonvulsant activity of the hydroalcoholic extract of *A. pyrethrum* root was investigated in both PTZ- and MES-induced epilepsy models in mice. Their results indicated that *A. pyrethrum* extract could possess significant anticonvulsant activity in both of these epilepsy models[20]. AEDs block the MES-induced tonic extension act by blocking voltage-dependent Na^+ channels. Hence, *A. pyrethrum* might have an inhibitory action against voltage-dependent Na^+ channels[25]. Moreover, previous studies have shown the antidepressant and memory-enhancing effects of *A. pyrethrum*26.

Paeoniae Radix (peony) is the dried root of *Paeonia lactiflora* which belongs to the Paeoniaceae family. Paeoniflorin, a monoterpene glycoside, is the most important pharmacologically active component of peony. Paeoniflorin possesses antioxidant, immunomodulatory, and anti-inflammatory effects[27]. Koyunoğlu et al. indicated that paeoniflorin displays an anticonvulsant activity in both MES- and PTZ-induced epilepsy models in mice[28].

1,2,3,4,6-penta-O-galloyl-beta-D-glucose (PGG) is another active component isolated from peony[29]. Viswanatha et al. reported that intraperitoneal administration of PGG in mice leads to potent anticonvulsant effects in both PTZ- and MES-induced convulsion models by increasing the GABA levels in the brain[30].

Tsuda *et al*.[31] demonstrated the protective effects of peony root extract on EEG changes and neuron loss in the cobalt focus epilepsy model. Previous studies have shown that the anticonvulsant property of *Paeoniae* Radix is due to albiflorin (another monoterpene glycoside) and PGG. Albiflorin and PGG inhibit the seizure-related decrease of extracellular calcium, and consequently inhibit the increase of the intracellular calcium concentration induced by PTZ[32].

Most of the AEDs have different activities against various seizure types. Moreover, there are some inconsistencies between the results of human and animal studies. This might be due to the limited understanding of the precise mechanism of drug action on receptors, which could underlie the failure to prove clinical efficacy and safety[17].

In TPM, these two medicinal herbs have been used alone or together to treat seizures. Combination treatment with drugs that have similar mechanisms of action could lead to additive efficacy, whereas it has been shown that polytherapy with AEDs that have different mechanisms of action creates synergistic effects[33].

Anticonvulsant drugs have many adverse effects such as cognitive, behavioral, and hepatic effects, and despite the regular and careful use of these drugs, these effects are not fully controlled in some children[34,35]. In the present study, 2.2% and 4.5% of the children became aggressive and restless, respectively. No abnormality was found in the LFT and CBC results in any of the patients. Previous studies have shown the excellent safety profile of *P. lactiflora,* when the whole plant is administered[36]. Earlier studies on the toxicity of *A. pyrethrum* root extract have shown no mortality, but significant changes in the body weight of animal models were reported18,37. However, in the present study, none of the patients reported this complication. Although there is a public belief about the safety of herbal medicines, some complications such as headache and increased sleep duration were reported during this study. However, it seems that the combination of *A. pyrethrum* and *P. lactiflora* could be tolerated in children.

Since this study was an uncontrolled before/after clinical trial, placebo-controlled studies with greater sample sizes are needed to more accurately assess the efficacy and safety of this traditional herbal formula. Moreover, EEG was not performed to evaluate the treatment outcomes, which is another limitation of the present study. In addition, future studies should restrict the seizure types to have more type-specific results.

Conclusion

According to the present study, the traditional preparation of *P. lactiflora* and *A. pyrethrum* could be considered as a complementary medicine for the treatment of childhood DRE. However, further studies are needed to provide more evidence of the benefits and possible harms of this preparation and also determine its precise mechanisms of action as a medicinal remedy for epilepsy.

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Conflict of Interest

The authors confirm that there is no conflict of interest.

Authors' Contributions

Conception and design of the study: MM, EN & MHN. Acquisition of data: SEM, FA & JA. Analysis and interpretation of data: MM, MS & MHN. Drafting the manuscript: MHN & MM. Revising the manuscript critically for important intellectual content: MHN & MM. All authors approved the submitted version of the manuscript.

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