Research Article **CODEN: AJPCFF** **ISSN: 2321 – 0915**

Asian Journal of Phytomedicine and Clinical Research

Journal home page: www.ajpcrjournal.com

THE ASSESSMENT OF ROSE ESSENCE (ROSA DAMASCENA) IN TREATING INTRACTABLE PHARMACORESISTANT EPILEPSY IN CHILDREN BETWEEN 3-12 YEARS

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ABSTRACT

Objectives: Epilepsy is a major neurological disorder among children. Rosa damascena is proven to have hypnotic, antispasmodic and relaxant properties. This study aimed to evaluate the effects of R. damascena essence on controlling intractable pharmacoresistant epilepsy in children between 3-12 years old admitted at the department of neurology of Ghaem Hospital. **Methods:** Simple random sampling was used in this study. Medical therapy was conducted in three stages. Initially, 500 cc of R. damascena essence was prepared and a concentration of 10% was obtained with medium-chain triglyceride (MCT). Afterwards, medical and placebo interventions were performed based on patients' referral prescription using a double-blinded approach. **Results:** In total, we studied 16 patients including 9 male (56.3%) and 7(43.8%) female subjects. There was a statistically significant difference between the frequency of seizures before and after the treatment with Rose oil (P=0.000). The seizures were suppressed in 3 cases (18.7%) and they completely receded in 12 patients (75%). Only in one case (6.25%), no significant differences were observed. **Conclusion:** Rosa damascena oil could significantly decrease the frequency of epileptic seizures. However, it may not affect the duration of the fits. Moreover, no side effects or complications have been associated with R. damascena as the adjuvant therapy for epileptic pharmacoresistant children.

KEYWORDS

Epilepsy, Pharmacoresistant and Rosa damascena.

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INTRODUCTION

Epilepsy is one of the most prevalent neurological conditions in which no such factors as age, racial status, social class, geographic situation or national boundaries are involved[1]. It affects 50 million people worldwide 80% of which live in the developing countries. An epileptic individual

suffers recurrent seizures provoked by acute brain insults or metabolic derangements[2,3].

Epilepsy is a common childhood condition associated with a considerable medical and psychosocial burden. Children in whom medical treatment fails to reduce the fits represent a particularly vulnerable population since prolonged, uncontrolled seizures are associated with poor developmental and neurocognitive outcomes[4-6].

Epilepsy is believed to be one of the most frequent neurological disorders in children with an approximate incidence of 45 per 100,000 per year[7-9]. Approximately 20% of epileptic children are known to be pharmacoresistant. The impact of intractable epilepsy extends far beyond seizures only to result in intellectual disability, psychiatric co-morbidity, physical injury, unexpected death during the fits and poor quality of life[10].

Various predictors for pharmacoresistance in epilepsy have been identified. However, the accurate prediction of the seizures is still a challenge for medical experts. Population-based epidemiological studies indicate that in children, pharmacoresistance tends to develop relatively early in the course of the disease. Nonetheless, approximately one third of the children who initially appear to be pharmacoresistant in the first few years after the onset of epilepsy will ultimately achieve seizure free without surgery[11,12].

First-line therapy for pediatric epilepsy consists of antiepileptic drugs (AEDs). Even so, the probability of seizure control diminishes with the increasing number of ineffective medications. In a prospective study of children with new-onset seizures, the first AED failed due to lack of efficacy in 25% of the patients[13] while 51% of these children showed a favorable response to the second agent of the drug. However, the chance of achieving remission of >1 year with subsequent regimens was only 29% after two AEDs had failed and 10% after three AEDs had failed[14].

In general, pharmacoresistance is defined as the failure of epileptic seizures to come under complete or acceptable control in response to AED therapy. Unfortunately, current AEDs may not prevent or reverse drug resistance in most patients while add-on therapy with novel AEDs might lead to a modest seizure reduction in up to 50% of the patients in short-term clinical trials, and a few might even become seizure free after the trial[15].

For children with pharmacoresistant epilepsy, there are other therapeutic options which could be largely effective at times. In cases with identified, surgically remediable epilepsy, resection is regarded as a viable option with up to 60-70% chance of seizure free. In addition, dietary therapy with the ketogenic diet might result in seizure free in 10-15% and worthwhile seizure reduction in more than half of the cases[16].

Approximately one third of the people with epilepsy (PWE) are known to have drug-resistant seizures[17,18]. Therefore, surgery is considered highly effective, as well as safe, for selected patients with treatment-resistant focal epilepsy. Nevertheless, surgery is still underused, even in high-income countries. Other treatment strategies are primarily palliative (e.g vagus nerve stimulation) or still under investigation (e.g closed-loop cortical stimulation)[19].

Although newer AEDs may offer an improved adverse-event profile in comparison to older-generation AEDs, they might still lead to significant central nervous system (CNS) defects such as decreased cognitive abilities and psychiatric complications. Evidently, more efficacious and better-tolerated treatments are to be modified for epilepsy. In this regard, complementary and alternative medication (CAM) has a long history of use in different parts of the world. Moreover, there has been a growing interest towards this approach in modern countries over the past decades[7].

In countries with a modern medical system, PWE tend to consume natural products or engage in other forms of CAM mainly to enhance general health as well as to prevent seizures and/or alleviate the symptoms of co-morbidities or side effects caused by antiepileptic medications[20]. Rosa damascena is a rose species which is famous for its desirable scent. Several studies have investigated its hypnotic, antispasmodic and relaxant properties as well as its

therapeutic effects on abdominal and chest pain and cardiac strengthening[21-23].

With respect to the importance of pediatric epilepsy and lack of adequate studies in this regard, we aimed to evaluate the effects of Rose (Rosa damascena) essence on controlling intractable epilepsy in pharmacoresistant children ageing from 3 to 12 years old who were admitted at the Department of Neurology of Ghaem Hospital in Mashhad, Iran.

MATERIAS AND METHODS

This was a cross-sectional, analytic and double-blinded study which was conducted at the Neurology Department of Ghaem Hospital. The inclusion criteria were as follows: 1) 3< age< 13 years; 2) normal renal, hepatic and ECG laboratory tests; 3) parents' consent and commitment to follow all the three test steps; 4) intractable epilepsy; 5) progressive cerebral disease; 6) lack of severe malnutrition, disabilities, systemic impairments and chronic renal, hepatic, endocrine, cardiac and gastrointestinal complications; 7) parents' availability.

In this study, we used simple random sampling. Since the ratio of intractable epileptic children accounted for 15-20% of the entire cases, 50 cases were required with a 95% accuracy coefficient and the maximum of difference in the real parameters of the study population. Furthermore, in the view of the fact that this study was the first conducted on this subject on human, we selected 20 children in order to prevent the possible complications of using the Rosa essence.

We recorded all the variables including age, gender, family history of epilepsy during infancy and childhood, the type of the first seizure or epileptic syndrome, Electrocardiogram (ECG), MRI findings and cerebral CT-scan. The medical therapy was performed in three stages.

Initially, 500 cc of Rosa damascena essence was prepared and afterwards, a 10% concentration was obtained by medium-chain triglyceride (MCT). The medicine and placebo were intervened based on the referral prescription using a double-blinded approach.

Since it was the first Rosa essence intervention, each patient was hospitalized at the Department of Pediatric Neurology in order to receive the placebo or medicine. First, we recorded the quantity and duration of each seizure. Afterwards, laboratory tests were performed including complete blood count (CBC), renal and hepatic tests, Electroencephalography (EEG) and ECG. Following that, the patients received the placebo and the medicine until possible complications appeared. In addition, CBC, serum glutamate-pyruvate transaminase (SGPT) and urea were measured after the patients received the droplet. One droplet per one kg of body weight was prescribed for younger children and 2 droplets per 2 kg of body weight for elder an child which was administered orally in 3 doses within 24 hours.

Pre-medicines continued for the cases and the droplet, randomly in the form of placebo or medicine, was administered to the patients. The patients remained hospitalized during the first days of the study as to assess possible complications. If no particular problems were observed, the patient would be discharged and the treatment would continue at their residence. The treatment process could briefly be classified into the following stages.

Prescription of medicine (A or B) in 3 doses for 10 days added to the patients' pre-medicine;

Discontinuing the droplet and continuing the previous drugs.

Prescription of the medicine (A or B) with the same dosage (1 or 2 droplets per each kg of the body weight administered orally in 3 doses) for 10 days.

At the beginning of each step, the children were kept hospitalized for 2-3 days in the department and the number and duration of each seizure would be recorded in each case. Moreover, the type of the seizure would be diagnosed observationally.

After collecting the data and the completion of the treatment, descriptive statistics were used to describe the observations by sorting the clinical and diagnostic characteristics and the field agents. Afterwards, all the collected data were analyzed by

Chi-square and nonparametric statistics of Wilcox on test, Friedman test and Pearson. Data processing was conducted by SPSS and Minitab software. In order to clarify the statistical findings, tables and diagrams were drawn as well.

RESULTS

Of all the 16 patients, 9 cases were male (56.3%) and 7 were female (43.8%). The mean age of the studied patients was 8.7 years (SD=3.7). The youngest patient was 2 years and the eldest was 13. The mean age of the first seizure incidence was 16.17 months (SD=15.7) with the minimum age of seizure incidence of 3 days and the maximum of 48 months old.

In 12 cases (75%), no history of epileptic seizures was detected while in 3 patients (18.8%), there was an epileptic history report in grade 2 relatives. In addition, 12 patients (75%) had been born via natural vaginal delivery and 4 (25%) were born via Cesarean section. The Apgar scores were in desirable condition in 13 patients (81.3%) during delivery while 3 cases (18.8%) did not score favorably.

The mean head circumference was 33.93 cm (SD=1.43) with the minimum size of 31 cm and the maximum of 36 cm. The head circumference of 12 children (60%) was under the normal range. The average birth weight was 3023.5 gr. (SD=279.1) with the minimum of 2300 gr. and the maximum of 3500 gr. Only 2 cases (12.5%) weighed under 2500 gr.

Neonatal epilepsy was diagnosed in 10 children (62.5%) while 6 cases (37.5%) were not reported to be epileptic. All the children received treatment with antiepileptic medicines 8 of which (50%) received 2 medicines, 6 (37.5%) received 3 and only one patient (6.2%) received 4 medicines.

Moreover, 9 children (56.3%) experienced different types of epilepsy; 7 cases (43.7%) had complex partial seizures, 4 patients (25%) had myoclonic seizures, Lennox Gastaut was observed in 2 subjects (12.5%), myoclonic epilepsy was detected in 2 patients (12.5%) and 2 cases (12.6%) had epilepsy with myoclonic absences.

Furthermore, the etiological assessment of the disease indicated that 2 patients (12.5%) had experienced traumatic brain injury (TBI), 5 (31.2%) had birth asphyxia, one (6.25%) suffered encephalitis, one (6.25%) had septicemia and one (6.25%) was with dysgenesis. As for other patients, no particular causes were reported.

The EEG of all the patients was indicative of epileptic changes while the CT-scan showed abnormality in 11 cases (68.8%). However, the abnormal results of CT-scan were not confirmed in 2 cases who had undergone MRI.

In the study group who used the Rosa essence, the number of repeated seizures reduced while no significant changes were observed in the duration of the fits.

According to the Wilcox on test, there was a significant difference between the time of essence prescription and before that regarding the frequency of seizures in different periods (P=0.007). Insert Table No.1.

Moreover, Friedman test was indicative of a statistically significant association between the frequency of seizures before and after the treatment with Rosa oil (P=0.000). The seizures were suppressed in 3 patients (18.7%), they completely receded in 12 patients (75%) and in only one case (6.25%) no significant differences were observed. insert Table No.2.

Furthermore, there were no significant differences between the placebo and the treatment group in terms of the following variables: age, gender, family history of seizures, neonatal history of seizures, Apgar scores, birth weight, head circumference, history of hospitalization, point of the first seizure, seizure syndrome and the type of epilepsy (P> 0.05).

According to the results of Kruskal-Wallis test, there was a significant difference between the number of seizures and the frequency of their type in both the placebo and the treatment group (P< 0.05).

No complications were observed after the treatment with Rosa essence and all the renal, hepatic and cardiac tests were normal.

DISCUSSION

Intractable pharmacoresistant epilepsy is a major medical issue in pediatric neurology. Despite new and developing pharmacologic approaches, the seizures are still present in a large number of epileptic patients and favorable therapies are rarely available. Trending to herbal medicine as an adjuvant therapy requires progressive academic research. In the current study, the effect of Rosa damascena on controlling intractable epilepsy was investigated in pharmacoresistant children of 3-12 years old. Several studies have confirmed the therapeutic impact of Rosa oil on epileptic seizures [24,25].

According to the results of the present study, a statistically significant association was observed between the frequency of seizures before and after the treatment with Rosa oil (P=0.000). The seizures were suppressed in 3 cases (18.7%), they completely receded in 12 patients (75%) and in only one case (6.25%), no differences were observed.

The main components of Rosa essence are linalool, eugenol, citronellal, damascenone and nerol[26].

In a double-blinded cross-over clinical trial, Akhondian et al (2010), evaluated the effects of Thymoquinone on intractable pediatric seizures. They administered Nigella sativa as an adjunctive therapy and observed a reduction in the frequency of seizures by the end of the first period of treatment[27]. Similarly, our findings were indicative of a decrease in the frequency of seizures in the treatment group.

Correspondingly, Ramezani *et al* (2008) claimed that the essential oil of R. damascena hinders the onset of epileptic seizures and reduces the duration of Tonic-clonic seizures in rats with acute pentylenetetrazol (PTZ) induced seizures (stage 4)[28]. Moreover, this plant could result in the prolongation of latent periods before generalized tonic-clonic seizures in the chronic form of PTZ-induced seizures[23].

In their study, Wie *et al* (1997) also reported that the geraniol and eugenol content of R. damascena essential oil possessed antiepileptic properties[29]. However, the actual mechanism of these compounds still remains unknown.

The effects of the essential oil of R. damascena as an adjunct therapy for children with refractory seizures have also been investigated and it has been proven that they result in a significant reduction in the mean frequency of seizures in the patients who receive the essence. Therefore, the essential oil of R. damascena is proven to have numerous beneficial antiepileptic agents in children with refractory seizures.

In another double-blind clinical trial conducted as a pilot study, Afsharzadeh *et al.* (2007) investigated the effects of essential Rosa damascena oil in 16 children with refractory epileptic seizures as an adjunct therapy[30]. They reported that the mean frequency of the seizures saw a significant decrease in the patients using the essence in comparison with the control group who were administered placeboes. They concluded that the essential oil of Rosa damascena had many beneficial antiepileptic effects on the children with refractory seizures. These findings are consistent with the results of the current study.

In our experiment, we realized that this method could be more effective, accessible, useful and cheaper compared to other alternative therapeutic methods such as ketogenic diet with 40-60% efficiency, vagus nerve stimulation with 30-40% efficiency and intravenous immunoglobulin with 30-50% efficiency.

Table No.1: The frequency of seizures in a period of 10 days, before and after adjuvant therapy by Rosa essence and placebo

S.No	The number of Seizure	Treatment period			
		Before essence	Time of essence	Before placebo	Time of placebo
1	0	-	3	-	-
2	1-5	-	3	-	2
3	5-10	6	2	6	4
4	10-20	1	2	1	1
5	20 <	9	6	9	9

Table No.2: Comparison of the quality of seizures in adjuvant therapy periods

S.No	Number of seizure	Period	
		Essence adjuvant therapy	Placebo
1	Suppressed	3(18.75%)	-
2	Decreased	12(75%)	7(43.75%)
3	No change	1(6.25%)	9(56.25%)
4	Total	16	16

CONCLUSION

Rosa damascena essence could significantly decrease the frequency of epileptic seizures. However, it does not affect the duration of the fits. Furthermore, no side effects or complications have been reported on the use of R. damascena as an adjuvant therapy in epileptic pharmacoresistant children.

ACKNOWLEDGEMENT

The authors appreciate the Research Council of Mashhad University of Medical Sciences for the financial support. The authors declare that there is no conflict of interests.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Farah Ashraf Zadeh, *et al*. The Assessment of Rose Essence (*Rosa Damascena*) in Treating Intractable Pharmacoresistant Epilepsy in Children between 3-12 Years, *Asian Journal of Phytomedicine and Clinical Research*, 3(4), 2015, 117 - 123.