Citicoline in the Treatment of Essential Tremor

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ABSTRACT

Objectives: To evaluate the clinical efficacy of Citicoline for the treatment of patients affected by essential tremor.

Methods: The study was conducted in the Neurology Department at King Hussein Medical Centre. A total of 18 subjects were non-randomly selected and enrolled in the study (8 males, 10 females), with a mean age of 62.6 years. The primary outcome measure was the degree of tremor compared to baseline as measured by the Clinical Rating Scale for Tremor.

Results: The mean duration of symptoms among the study group was 6 years. All patients were evaluated at least twice, at enrollment and 8 weeks after starting treatment. The dose was 2ml twice daily (equivalent to 400mg /daily) taken orally. Seven subjects showed marked improvement on Clinical Rating Scale for Tremor. Seven subjects showed moderate improvements, and 2 subjects showed mild improvement, and two subjects showed no change. The overall improvement in all treated subjects was 89% (T-Value = 8.42, P-Value = 0.000). The main side effects encountered during the treatment period were gastrointestinal symptoms in two subjects (11%), anxiety in one subject (6%), headache in one subject (6%), dizziness in one subject (6%), and insomnia in another (6%).

Conclusion: Citicoline significantly improved essential tremor in this small group of subjects.

Key words: Citicoline, Essential Tremor

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Introduction

The pharmacologic therapy for essential tremor (ET) is unsatisfactory in many patients. Citicoline is a naturally occurring compound that is essential for the synthesis of phosphatidylcholine. It also enhances the synthesis of acetylcholine and restores phospholipid content in the brain.

ET is one of the most common movement disorders but relatively few effective and tolerable therapies are available.[1] It is a sporadic or familial disorder characterized by postural and/or kinetic tremor affecting mainly the arms, and less frequently it can affect other parts of the body such as the lower limbs, head, and voice.[2] In advanced stages, daily living activities, such as eating and writing, may become impaired.[3] Although the pathophysiological basis of ET is controversial,[4] several recent studies showed that there are identifiable structural pathological changes in ET in post mortem brains.[5-11] These changes were either cerebellar degenerative changes, including increase numbers of torpedoes (*i.e.*, proximal swelling of the Purkinje cell axon), with reduction in number of Purkinje cells, or the presence of Lewy bodies in the locus cereleus.[12]

ET treatment have shown limited efficacy, particularly in patients with severe and disabling symptoms. The main two drugs which have been

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proven equally effective in ET therapy are propranolol and primidone.[13] Several other drugs have been used with limited or short lasting efficacy.[14-21]

Our study aimed to evaluate the clinical efficacy of Citicoline for the treatment of patients affected by ET at King Hussein Medical Centre.

Methods

An open study was conducted to evaluate the efficacy of Citicoline for the treatment of ET in the Neurology Department at King Hussein Medical Centre between February 2009 and July 2009. We assessed a group of 18 patients (8 males, 10 females) who met the diagnostic criteria of ET as proposed by Bain *et al*.[22] Females constituted 55.6% of the study group and the sample's age ranged between 44 and 76 years (mean 62.6 years), (Table I).

Their mean duration of illness was 6 years (range 1–14 years), and 7 out of 18 (38.8%) showed positive family history associated with ET. The patients who were on specific medication for ET were stopped for two weeks before the beginning of the study. All patients proved to have normal thyroid function tests prior to enrollment. All 18 patients had bilateral tremor in the upper extremities. None of the studied patients were taking alcohol. All patients received Citicoline in an oral dose of 2ml twice daily (equivalent to 400 mg daily) during the study period. An informed consent was obtained from all patients before the study in addition to Institutional Review Board (IRB), and Institutional Ethical Committee (IEC) approval.

The severity of tremor was quantified using the Clinical Rating Scale for Tremor (CRST).[23] All clinical evaluations were carried out and recorded by neurologists.

All patients were clinically evaluated at least twice, at enrollment and 8 weeks after starting treatment using the CRST. The degree and percentage of improvement on CRST was scored: no improvement, mild improvement (up to 30%), moderate improvement (31-50%), and marked improvement (above 51%) as illustrated in Table II. Simple descriptive statistics using mean and percentage was used to describe the study variables. T-test was used to determine statistically significant baseline and post treatment improvement after Citicoline treatment.

Results

Table III demonstrates that seven subjects showed marked improvement on CRST (39%), seven subjects showed moderate improvements (39%) two subjects (11%) showed mild improvement, and two subjects showed no change (11%). The overall improvement in all treated subjects was 89%.

A statistically significant difference was found for most of patients when comparing basal and post treatment evaluations ($t = 8.42$, $P = 0.000$). No statistically significant differences were found between those patients with family and those without family history in terms of response.

Throughout the study, treatment with Citicoline showed a tolerability profile that seemed favorable in all cases, with no drop outs. Table IV presents the main side effects encountered during the treatment period which were gastrointestinal symptoms in two subjects (11%), anxiety in one subject (6%), headache in one subject (6%), dizziness in one subject (6%), and insomnia in one subject (6%).

Discussion

The last few years have seen an increase in the number of therapies studied for ET. Nevertheless, the drug treatment of ET remains poor and often unsatisfactory,[24] and most studies support, at best, a 50% reduction in tremor severity.

The report of the Quality Standards Subcommittee of the American Academy of Neurology published in 2005:[25] recommended propranolol and primidone for limb tremor as level A; Alprazolam, Atenolol, Gabapentin, and Topiramate as level B; Clonazepam, Nadolol, clozapine, Botulinum toxin A, and Nimodipine, Deep Brain Stimulation (DBS) and Thalamotomy as level C.

The efficacy of Primidone and b-adrenergic antagonists such as Propranolol has been demonstrated in several studies,[26-29] and considered by many as first line of treatment.[25] Gabapentin on the other hand can be likely regarded as an appropriate treatment in ET as it has shown improvement in several studies,[30-32] and may have similar efficacy to propranolol.[30] Several double-blind placebo controlled trials of Topiramate in ET subjects showed improvement in subjective and objective measurements of tremor corresponding to 20%–30% improvement over baseline.[33-35] Two open-label studies showed modest benefit of Zonisamide in the treatment of ET.[36-38] A double-

Table I. Demographic Characteristics of Patients

Subject	Gender	Age	Duration of symptoms in years	Positive Family History
1	F	72	11	
2	M	61	4	+ve
3	F	55	12	+ve
4	F	48	3	
5	F	57	2	+ve
6	M	59	1	
7	M	76	5	
8	F	44	14	+ve
9	F	66	3	
10	F	69	5	+ve
11	M	70	1	+ve
12	M	72	6	
13	F	76	5	
14	M	46	7	
15	F	64	3	
16	M	61	12	+ve
17	M	66	9	
18	F	65	5	

Table II. Clinical Evaluation of Essential Tremor (ET) before and after eight weeks of treatment with Citicoline

Subject	Baseline tremor rating scale (0-4)	Tremor rating scale at 8 weeks (0-4)	Percentage of improvement from baseline	Degree of improvement
1	3	1	50	***
2	2	0	100	****
3	4	2	50	***
4	2	0	100	****
5	1	0	100	****
6	1	0	100	****
7	2	1	25	**
8	4	2	50	***
9	2	0	100	****
10	3	3	0%	*
11	2	1	50	***
12	3	1	50	***
13	3	2	25	**
14	3	3	0	*
15	2	0	100	****
16	4	1	75	****
17	3	1	50	***
18	3	1	50	***

Clinical Rating Scale for Tremor (CRST): 0= no tremor, 1= slight, may be intermittent, 2= moderate amplitude, may be intermittent, 3= marked amplitude, 4= severe amplitude

Degree of Improvement: * = no improvement, ** = mild improvement (up to 30% improvement), *** = moderate improvement (31-50% improvement), **** = marked improvement (above 51%)

blind placebo controlled study using Pregabalin showed significant benefit in reduction of tremor amplitude.[39]

Botulinum Toxin has also been studied in ET,[40-45] most studies have demonstrated mild to marked improvement over baseline in terms of clinical rating scales.

Citicoline is a complex organic molecule that functions as an intermediate in the biosynthesis of cell membrane phospholipids. Citicoline is also known as CDP-choline and cytidine diphosphate choline (cytidine 5'-diphosphocholine).

Exogenous Citicoline is hydrolyzed in the small intestine and readily absorbed as choline and cytidine, where they enter various biosynthetic pathways that utilize Citicoline as an intermediate, and cross the blood-brain barrier for resynthesis into Citicoline in the brain. Citicoline was found to have a sparing effect on systemic choline reserves, as well as inhibiting the breakdown of membrane phospholipids. The brain uses choline preferentially for acetylcholine synthesis, and when the demand for acetylcholine increases or choline stores in the brain are low, phospholipids in the neuronal

Table III. Number and percentage of improvement after receiving Citicoline among the study group

Degree of Improvement	Number of Patients	Percentage of Improvement
No Improvement	2	11
Mild Improvement	2	11
Moderate Improvement	7	39
Marked Improvement	7	39

Table IV. Side effects among the study group

Side effect	Anx	LE	Dep	H	N, V, D	INS	EBT	ALG	UI	DIZ
1					*					
2										
3										
4	*			*						
5										
6										
7										
8										
9										
10					*					
11										
12										
13										*
14										
15										
16						*				
17										
18										

EBT: elevated body temperature, **H**: headache, **N, V, D**: nausea, vomiting, diarrhea, **Anx**: anxiety, **Dep**: depression, **UI**: urinary incontinence, **INS**: insomnia, **ALG**: Allergic reaction, **LE**: Leg Edema, **DIZ**: dizziness

membrane can be catabolized to supply the needed choline.

In an in-vitro study, Citicoline at high concentrations stimulated brain acetylcholinesterase (AChE). The postulated mechanism involves bioconversion of Citicoline to phosphatidylcholine. Experimental studies in rats found evidence that Citicoline potentiates dopamine release in the brain, presumably by stimulating release of acetylcholine.[47] As the Biochemical markers of cholinergic nerve transmission are known to be deficient in conditions characterized by degeneration of cholinergic neurons, such as Alzheimer's disease (AD), Citicoline was found to modestly improve cognitive function in these patients by serving as an acetylcholine precursor.

Citicoline has been used in various disorders mainly neurological, in particular stroke, brain injury, Alzheimer's Disease, and vascular dementia.

A study carried by Agnoli *et al.* using CDP-Choline in Parkinsonian patients based on its intermediate action in the phospholipid metabolic pathway to improve the functionality of the dopamine (DA) system, showed that CDP-choline significantly improve rigidity and bradykinesia with less amelioration of tremor suggesting a possible action on the DA receptor through an activation of the phospholipid metabolism.

In our open experimental study, we found that Citicoline is an effective drug in the control of tremor symptoms in a dose of 400mg daily. The overall improvement was in 89% in the study group, which is higher than any previous studies conducted to date to control ET. If we compare our result to Propranolol which is the only FDA approved medication for ET, we find that the mean reduction of tremor in propranolol ranged from 50-60%[25] whereas with Citicoline it reached 89%.

The improvement was marked in 39%, moderate in 39%, and mild in 11% and in 11% showed no benefit**.** Although no benefit was noted clinically in two subjects (11%), the two non-responders believed that they felt subjectively better and wished to continue the treatment.

Limitation of the Study

Comparison of our study results regarding efficacy of Citicoline in ET treatment is different because of the study design and population selection. Further studies, preferably double-blind and placebo

controlled, are needed to find out the role of Citicoline in the treatment of various types of tremor.

Conclusion

Citicoline significantly improved essential tremor in this small group of subjects.

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