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Comparison of Treatment Effect of Sodium Valprovate, Propranolol and Tricyclic Antidepressants in Migraine

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Abstract: This study was conducted to evaluate and compare the efficacy and treatment effect of sodium valprovate with propranolol and tricyclic antidepressive drugs. This piece is a rarandomized clinical trial conducted on 126 migraine patients admitted to brain and nerves clinic in Arak, Iran. Patients were divided in two groups then randomized to study treatments. Data were gathered using a checklist and a complete examination. They were analyzed by Chi square and exact test. In patients with normal and abnormal encephalogram the effectiveness rate of two treatments were 35, 61.9, 95.6 and 28.6%, respectively. This difference between two treatments was statistically significant ($p<0.001$). But didn't observe significant differences between two sex groups ($p>0.05$). For treatment and control of the migraine, in patients with normal encephalogram, propranolol with tricyclic antidepressive drugs advised and for abnormal encephalogram sodium valprovate can be the better treatment for management and reduction of headache attacks.

Key words: Sodium valprovate, tricyclic antidepressants, encephalogram, migraine

INTRODUCTION

Migraine is a common chronic daily headache disease characterized by repeated episodes of head pain that can be caused frequent and severe attacks of headaches (Spasic *et al*., 2003; Calabresi *et al*., 2007; Silberstein *et al*., 1996). Among the primary headaches, migraine is identified as the most contributor in general people (Silberstein, 2006). Over 80% of these people suffer some degree of headache-related disability (Stewart and Lipton, 1993). The annual prevalence of this debilitating neurological disorder (Lipton *et al*., 2001) that is 12% for adults and ranged from 6% in men and 18% for women (Spasic *et al*., 2003; Lipton *et al*., 2001). The lifetime prevalence of disease within United States women exceeds from 25%, so one of four women affected by migraine at life duration (Lipton *et al*., 2001; Diamond *et al*., 2007) and the estimated annual cost, including costs of direct medical care and lost productivity, exceeds $17 billion in this country (De Lissvoy and Lazarus, 1994).

Although, over half of the patients didn't diagnose or are taking a treatment (Lipton *et al*., 2001), more than 90% of patients with migraine have disability with their attacks and half these patients need to rest in bed (Mueller, 2007). Despite of high prevalence, because of undiagnosing or misdiagnosing of migraine it has been demonstrated that the disease has a significant impact on treatment, disability and quality of life, so early recognition and treatment is necessary (Hershey and Winner, 2005).

Several medications have been developed to establish efficacy of some treatments in migraine (Owens *et al*., 2008; Silberstein, 2000), such as valprovate sodium, valprovate acid, dopamine antagonist and tricyclic anti depressive and other drugs that were using for reduction or limitation of frequency and intensity of migraine (Hershey and Winner, 2005). However, migraine headaches have a great impact on disability and quality of life, so early recognition and treatment is necessary (Unalp *et al*., 2008).

There are many randomized clinical studies that ascertained the effect of valprovate sodium in reducing severity and duration of migraine attacks. For example, Unalp *et al*. (2008) reported that valproate able to manage successfully migraine as well as shaygannejad has previously been shown the effect of sodium valprovate in reduce migraine headache (Yurekli *et al*., 2008). Also, Spasic *et al*. (2003) approved the efficiency of valproate in prevention and treatment of patients with migraine by significant reduction in frequency, intensity and mean of episodic duration of attacks. In addition several studies ascertain the effective impact of tricyclic antidepressive drugs in management of migraine (Levinstein, 1991; Hershey *et al*., 2000).

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Therefore, we designed and conducted this study to evaluate and compare the efficacy and treatment effect of sodium valprovate with propranolol and tricyclic antidepressive drugs in a clinical controlled randomized trial based on encephalogram test.

MATERIALS AND METHODS

This present randomized controlled clinical trial conducted on 140 admitted patients to brain and nerves clinic at Valiasr hospital of Arak, Iran. From all of them 126 subjects (40 male and 86 female) have inclusion criteria and enrolled for study. The study was carried out on 10-50 years old patients with the equal portion in each age and treatment group. Participants have been completed in 6 month, from March 2002 to August 2002.

Collection of data was conducted with a checklist that involves complete examination results such as encephalogram and computerized tomography scan of brain, blood exam and kidney and liver function. Then analyzed by chi square and fisher exact test in SPSS software, the values of less than 0.05 have been considered as significant level.

Inclusion criteria were patients with upper 10 years old and whom that permitted for use of treatment base of blood exam and kidney and liver function, so patients under 10 years old and whom can't take study drugs due to blood, kidney and liver function exams exclude from study. Also unintention in participations for concluding in study and have any pathologic damage were the exclusion criteria.

Patients divided in two groups based on normal and abnormal encephalography, then each group randomized in to one of treatments methods. (1) valprovate sodium pill (15 mg kg^{-1}) 1-3 pills daily and (2) propranolol pill (40 mg) 1-2 pills daily with 50 mg amitriptyline or 25 mg nortriptyline (1-2 pills daily).

In the study period checking for blood exam, kidney and liver function, effect of drugs on frequency, severity and period of migraine attacks, drugs side effects such as vertigo, vomiting, nausea, depression and fatigue feeling at third month conducted in participations, for change in dosage or treatment type, if the result of these examinations have been shown any side effect. The study protocol has been approved by ethical committee of the Arak University of Medical Sciences.

RESULTS

forty patients (31.8%) were male and 82 patients (65.1%) have a normal encephalogram. encephalogram taken for each patient, then computerized tomography scan of brain performed too, but didn't observe any pathologic damage in patients.

Table 1: Frequency distribution of migraine patients base of amelioration status, encephalogram and treatment type

	Patient status		
Treatment type	Without amelioration	Complete amelioration	p-value
Normal encephalogram			
Valprovatesodium	14 (35)	26 (65)	<0.001
Propranolol and anti depression	26 (61.9)	16 (38.1)	
Abnormal encephalogram			
Valprovate sodium	22 (95.6)	1 (4.4)	<0.001
Propranolol and anti depression	6 (28.6)	15 (71.4)	

Values in brackets are percentage

Table 2: Frequency distribution of side effects of two treatments method in patients

	Side effects				
Drug	Fatigue feeling	Depression	Vomiting	Nausea	Vertigo
Valprovate sodium	9 (14.3)	6 (9.5)	4 (6.3)	4 (6.3)	17 (27)
Propranolol and anti depression	6 (9.5)	5 (7.9)	2 (3.2)	3 (4.8)	2 (3.2)

Values in brackets are percentage

As indicated in Table 1 in normal encephalogram group, 40 patients (48.8%) consumed valprovate sodium and 42 patients (52.2%) consumed propranolol with amitriptilin or nortiliptilin, the effectiveness ate of these treatments were 35 and 61.9%, respectively. This difference between two treatments was statistically significant ($p<0.001$).

Among the 44 patients (34.9%) with abnormal encephalogram, 23 patients (52.3%) consumed Valprovate sodium and 21 patients (47.7%) consumed propranolol with Amitriptilin or Nortiliptilin that effectiveness rate of these treatments were 95.6 and 28.6%, respectively. This difference between two treatments was significant statistically ($p<0.001$).

The amelioration rate in males and females was 54.6 and 52.5%, also this rate in patients with normal and abnormal encephalogram was 48.8 and 63.6%, respectively. There weren't any statistically significant differences between male and female patients as between patients with normal and abnormal encephalogram ($p>0.05$).

The amelioration rate in patients that treated with valprovate was 57.1% and this rate in patients that treated with propranolol with amitriptilin or nortiliptilin calculated 50.8%, this difference was significant statistically ($p<0.001$).

As shown in Table 2, the most common side effect for valprovate was vertigo and in patients that treated with propranolol with amitriptilin or nortiliptilin was fatigue feeling.

DISCUSSION

The result of this study showed that encephalogram can be considered as a diagnostic test for migraine; because after conducting encephalogram test, computerized tomography scan of brain tested in whole patient didn't show any pathologic damage in the patients brains. However, it has been reported that encephalogram caused an encephalopathy in a 11 old year child (Topczewski *et al*., 2008). Therefore, it is recommended to use this diagnosis method cautiously due to the adverse effects of radiation.

Another result of our study showed that in patients with normal encephalogram, Valprovate sodium can consider as a good treatment and based on these results. Several study (Yurekli *et al*., 2008; Pascual *et al*., 2007) approved the efficacy of sodium valprovate and its derivatives in management of migraine. A double-blind, randomized, placebo-controlled trial that conducted as parallel design approved the efficacy of the extended-release version of VPA recently (Freitag *et al*., 2002).

Other results of present study showed that in patients with abnormal encephalogram, propranolol and tricyclic antidepressive drugs have an impact in amelioration of patients. Two studies (Levinstein, 1991; Hershey *et al*., 2000) showed that tricyclic antidepressive drugs have a good effect in reduction of frequency and intensity of migraine. In a crossover study that used tricyclic antidepressive for headache prevention, comparing amitriptyline with propranolol and cyproheptadine, Levinstein (1991) showed that amitriptyline to be effective in 50 to 60% of the children. Also in another (Hershey *et al*., 2000) clinical study ascertained that amitriptyline hydrochloride caused a perceived improvement in more than 80% of the children, with a subsequently decreasing headache frequency and impact on the migraine. But it is considerable that the effect of tricyclic antidepressive may cause the better amelioration in children.

In present study, amelioration rate due to sodium valprovate in males and females, normal and abnormal encephalogram was 54.6 and 52.5%, 48.8 and 63.6%, respectively. Present results was same to other studies, as Freitag *et al*. (2002) reported 52-59% improvement in their study. Although, seems the same result with our finding but it is necessary that consider about differential dosage and duration of intervention in two study.

Assessing the adverse effects of these treatments in patients showed that all of these side effects such as vertigo, fatigue feeling, depression, vomiting and nausea were higher than in valprovate arm. In other study (Yurekli *et al*., 2008) somnolence and fatigue feeling was also a most important side effect of sodium valprovate.

CONCLUSION

Results of this study suggest that in neurological clinics, for treatment and control of the attacks in migrainic patients, first screening by encephalogram test should be done and then divided in two normal and abnormal groups. For normal encephalogram group, propranolol with tricyclic antidepressive drugs advised and for abnormal encephalogram group sodium valprovate can be the better treatment for management and reduction of headache attacks.

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