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Comparison of botulinum toxin type-A and divalproex sodium for prevention of chronic and episodic migraine

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Abstract

Background & Objective: There is a need for a more effective and better tolerated prophylactic treatment of migraine. This study aims to compare the efficacy of botulinum toxin type-A (Dysport) and divalproex sodium (divalproex) as prophylactic treatment in patients with episodic or chronic migraine. *Methods*: This was a randomized, cross-over, single-center clinical trial. Participants were randomly divided into two treatment groups. Two phases of intervention were arranged (each for three months). In the first phase, patients received either Dysport (125 units) or divalproex (200 mg bid for three months). The patients were left for a three months washout period, and then the treatment agents were swapped in the second stage. The response to each treatment was assessed at the end of each phase. *Results:* With divalproex, the frequency, intensity and duration of headache, as well as analgesic consumption were significantly reduced ($p<0.05$) in both episodic and chronic patients. However, Dysport demonstrated significant efficacy only in patients with episodic migraine. In chronic migraine, Dysport only showed a non significant trend to benefit in these parameters, with exception of headache intensity,where it resulted in significant improvement from baseline. Divalproex was significantly superior to Dysport, in terms of headache frequency and intensity in patients with episodic migraine.
Conclusions: Both Dysport and divalproex are effective prophylactic therapies for patients with episodic migraine. Divalproex but not Dysport was significantly effective for chronic migraine.

INTRODUCTION

Migraine is a common cause of disability worldwide, with a rate of 17.6% in females and 5.7% in males.[1] Migraine can impair the quality of life, and also can disturb daily activities and work-related efficiency.[2] Therefore, prevention for migraine headache is reasonable and justified. Preventive management is divided into pharmacologic and non-pharmacologic treatments.[3] The most common pharmacological agents used for prevention of migraine headache include; β-blockers, calcium-channel blockers, tricyclic anti depressants, monoamine oxidase inhibitors, and anticonvulsants.[4-7] These pharmacological agents may have a restricted efficacy, and be associated with several side effects in long-term consumption that may lead to poor compliance.[8] Divalproex sodium (divalproex) is an anticonvulsant agent with GABA-mimetic effects[8], that has been used for the treatment of headache. In literature, about 30% to 50% of patients treated with divalproex have shown 50% of decrease in the frequency of their headache.[9-11] Reported side effects by Divalproex include: weight gain, alopecia, nausea, somnolence, tremor, disequilibrium, and rash.[12] Another accepted prophylactic treatment for migraine headache is botulinum toxin type-A.[13] It was initially utilized for the release of facial wrinkles and was incidentally found to lessen migraine headache.[14] Several studies of the effect of botulinum toxin type-A or divalproex on chronic and episodic migraine headache[15-23], have come to variable and even diverse conclusions. Only one study has directly compared botulinum toxin type-A with divalproex for the treatment of both chronic and episodic migraine.[15] The purpose of

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our trial was to compare the efficacy and safety of Dysport (botulinum toxin type-A) with divalproex on chronic or episodic migraine. The primary endpoint of this study was the reduction in the frequency of headache per month.

METHODS

We performed a randomized, crossover, single-blind clinical trial, without placebo control, however, with active components to compare the effect of Dysport and divalproex as preventive treatments of chronic or episodic migraine. This single-center, study was conducted in the neurology clinic of Al-Zahra Hospital, Isfahan, Iran, from October 2010 to September 2011. Sequential patients with chronic or episodic migraine (according to International Headache Society (IHS) criteria)[24], who were seeking for a preventive treatment were recruited to this study. Chronic migraine was defined as equal or more than 15 days with migraine headache per month and episodic migraine was defined as equal or more than 4 but less than 15 days with migraine headache per month. The primary end point was the reduction in the frequency of migraine headache. Doctrines of current version of the declaration of Helsinki were observed.[25] The Ethics Committee of Isfahan University of medical science approved the study, and the trial design and potential side effects of the drugs were elucidated for patients. After a comprehensive conversation by neurologist, to assess the inclusion and exclusion criteria, eligible patients who had signed the informed consent were enrolled into the study.

Inclusion Criteria

The inclusion criteria were: (1) Migraine headache frequency of 4 or more attacks per month during the past three months before entering the study; (2) Availability in the following 10 months; (3) Male or female, between 18 and 60 years of age.

Exclusion Criteria

The exclusion criteria were: (1) Females who were pregnant, breast feeding, or planning for pregnancy; (2) Patients with headache disorders other than chronic or episodic migraine headache; (3) Patients with serious medical conditions; (4) Patients with significant liver or renal impairment; (5) Patients, who had received botulinum toxin-A or divalproex in the last three months before the study; (6) Concurrent prophylactic treatment for migraine; (7) Use of any antidepressant or other drugs with potential preventative effects on headache within three months before the study.

A total of 36 consecutive eligible participants were randomly allocated into two treatment groups. A baseline evaluation was performed including demographic data, frequency, intensity, and duration of headache and number of analgesic consumption. Two phases of intervention, each for three months, were arranged. In the first round, the first group received Dysport 125 units (1/5 for each temporalis muscle, 1/5 for each frontalis muscle and 1/5 for glabellas region) and the second group received divalproex (200 mg twice daily) for three months with 10 weeks full dose and 2 weeks taper. After a three-month washout period, the treatment agents were swapped, and the second phase was carried out. Each patient received a daily headache diary to be filled out during the study. The response to treatments was assessed at the end of each round and moreover, patients were evaluated for any related side effects. During the study, patients were allowed to use analgesic if necessary.

All evaluations were made by an expert neurologist in migraine who was blind regarding to the type of intervention. A 10 points Visual Analog Scale (VAS) was utilized to determine the intensity of headache (0 indicates no pain, and 10 indicates the most intense pain). Every effort was taken to encourage patients wishing to leave the trial early to continue till the completion of the trial.

Statistical Analysis

All data was entered into a computer. To compare the patients receiving Dysport and divalproex, Student's t-test was used for independent sample which is suitable for the crossover studies. Comparisons between baseline assessments and results at the end of each phase were made by a paired Student's t-test, while the Chi-square test was employed for comparisons between side effects.

Results are presented as mean standard error. A P-value of <0.05 was considered statistically significant. Computerized data were analyzed using SPSS 18 software.

RESULTS

Thirty six patients who met the entry criteria were enrolled into the study. Thirty five patients completed the trial (26 episodic and 9 chronic patients). Nineteen were female (54.3%) and sixteen (45.7%) were male. The mean age was

Table 1: Baseline characteristics of patients

	Total N=35		Group 1 N=18		Group 2 N=17		Groups differences (p value)	
	Episodic n=26	Chronic n=9	Episodic n=13	Chronic n=5	Episodic n=13	Chronic n=4	Episodic	Chronic
Frequency of Headache (day per month)	6.96 ± 0.42	16.22 ± 0.36	6.85±0.57	16.20±0.49	7.08±0.59	16.25±0.62	0.76	0.97
Headache intensity (VAS)	6.42 ± 0.33	9.11 ± 0.5	6.31±0.59	8.80±0.80	6.54±0.35	9.50±0.28	0.72	0.54
Duration of each attack (hours)	17.77 ± 1	26 ± 1	18.46±1.85	26.40±1.47	17.08±1.33	25.50±1.5	0.51	0.80
Analgesic consumption (pill per attack)	2.54 ± 0.2	3.78 ± 0.3	2.62±0.31	3.80±0.49	2.46±0.24	3.75±0.25	0.69	0.94
Male	12	4	6	2	6	2	0.99	0.99
Female	14	5	7	3	7	2	0.99	0.99
Age	39.6±2.36	48.1±2.24	38.6±2.29	50.2±2.08	40.6±2.53	46±1.08	0.52	0.43

41.85 years (ranged 25-57). The characteristics of the patients at baseline are shown in Table 1. There were no significant differences in demographics or baseline characteristics of the two treatment groups.

Headache frequency

In patients with episodic migraine, the average of headache frequency decreased from the baseline by -3.65±0.2 Days for divalproex (p =0.001), and -3.19±0.2 Days for Dysport (p =0.001). This reduction was significantly higher for divalproex compared to Dysport (p =0.005). In patients with chronic migraine, the average of headache frequency decreased from the baseline by -5.77±1.2 days for divalproex (p =0.002), and by -2.44±1.2 days for Dysport (p =0.09). The difference between divalproex and Dysport was not statically significant (p =0.06).

Headache intensity

In patients with episodic migraine, the headache intensity decreased from the baseline by -1.615±0.2 VAS score for divalproex (p =0.001), and by -1.19±0.2 VAS score for Dysport (p =0.001). This reduction was significantly higher for divalproex compared to Dysport (p =0.009). In patients with chronic migraine, the headache intensity decreased from the baseline by -1.33±0.3 VAS score for divalproex (p =0.004), and by

Table 2: Changes in headache characteristics after intervention.

		Frequency	intensity	Duration	Analgesic
Episodic	**After Dysport**	3.77 ± 0.35	5.23 ± 0.3	13.38 ± 1	2 ± 0.2
	After divalproex	3.31 ± 0.3	4.81 ± 0.3	11.77 ± 1	1.88 ± 0.2
	Differences	0.46±0.1(p=0.005)	0.42±0.1(p=0.009)	1.61±0.8(p=0.07)	0.12±0.1(p=0.26)
Chronic	**After Dysport**	13.78 ± 1.5	7.67 ± 0.8	22.6 ± 2.1	3.56 ± 0.4
	After divalproex	10.44 ± 1.6	7.78 ± 0.7	19.33 ± 1.5	3.33 ± 0.3
	Differences	3.33±1.5(p=0.06)	0.11±0.2(p=0.68)	3.33±2.4(p=0.2)	0.23±0.2(p=0.34)

-1.44±0.4 VAS score for Dysport (p =0.008). No significant differences were noted between Dysport and Divalproex (p =0.68).

Headache duration

In patients with episodic migraine, the duration of headache decreased from the baseline by -6±0.7 hours per attack for divalproex (p =0.001), and by -4.38±0.8 hours per attack for Dysport (p =0.001). The differences between divalproex and Dysport was not statistically significant (p =0.07). In patients with chronic pattern, the duration of headache decreased from the baseline by -6.66 ± 1.8 hours for divalproex (p =0.007), and by -3.33±1.7 hours for Dysport (p =0.09). As with the patients with episodic migraine, the difference between divalproex and Dysport was not statistically significant (p =0.2).

Analgesic consumption

In patients with episodic migraine, the number of analgesic consumption for each attack, decreased from the baseline by -0.65±0.1 pills for divalproex (p =0.001), and by -0.53±0.1 pills for Dysport (p =0.001). The difference between divalproex and Dysport was not statistically significant (p =0.26). In patients with chronic migraine, the number of analgesic consumption for each attack, decreased from the baseline by -0.44±0.2 pills for Divalproex (p =0.03), and by -0.22±0.14 pills for Dysport (p =0.16). As with the patients with episodic migraine, the difference between divalproex and Dysport was not statistically significant (p =0.34).

Adverse effects

Both Dysport and divalproex treatments were well tolerated, with some mild transient side effects that only led to one Dropout as a consequence of divalproex side effects. For Dysport, adverse events were reported in 11 patients. The most frequently reported adverse events associated with Dysport were ptosis (8 patients) and blurred vision (4 patients). For divalproex, adverse events were reported in 23 patients. The most common were gastrointestinal upset (13 patients), fatigue (8 patients), weight gain (7 patients) and dizziness (5patients). Generally, the incidence of side effects was higher in patients who received Divalproex (63.9% vs.30.6%; P<0.001, Chi- square).

DISCUSSION

This was a crossover single-blind study without placebo control. To the best of our knowledge this is one of the few randomized, controlled assessments of Dysport and divalproex for the prophylactic treatment of both chronic and episodic migraine headaches. Our findings revealed a comparable efficacy of Dysport and divalproex as two good preventive treatments for episodic migraine headache. divalproex showed superiority to Dysport in terms of frequency and intensity reduction in patients with episodic migraine headache, but not in other measurements. In chronic migraine patients, we observed a significant improvement for divalproex in all evaluated headache characteristics. However improvement was obtained only with respect to headache intensity when Dysport was used in in patients with chronic migraine. Our findings in the primary study endpoint (frequency) are compatible with finding of previous studies.[15,26]

Variable results have been presented about effectiveness of botulinum toxin type-A as a prophylactic treatment for migraine. Unlike our study, several studies have reported the effectiveness of Dysport in patients with chronic migraine[16,18,19,27], however the design of these studies differ from ours. The pooled results of two studies with more than 1000 chronic migraine patients, has shown the efficacy of botulinum toxin type-A as a good prophylactic agent for chronic migraine headache. Compared to placebo, botulinum toxin type-A was associated with a significant improvement in headache parameters, a significant reduction in headache disability and therefore, improved function and quality of the life.[16] Another trial by Relja for the prevention of episodic migraine headache showed botulinum toxin type-A as a safe and tolerable treatment but without a significant superiority over placebo.[28] However, as with our study, numerous investigators have estiablished the effectiveness of divalproex.[8-11,29-31] In our trial, the lack of significant improvement in the chronic migraine group receiving Dysport might have been caused by the small sample size (n = 9), and cannot be considered to be conclusive. Although both Dysport and divalproex resulted in comparable benefits in this study, they showed diverse side effects. The rate of side effects for divalproex was almost twice as Dysport and led to one dropout (alopecia) compared to no dropout for Dysport. The most frequently reported side effects were ptosis for dysport and gastrointestinal upset for divalproex.

In conclusion, the results of our trial show that Dysport and divalproex are both effective

and comparable prophylactic therapies for patients with episodic migraine headache. In addition, in chronic migraineurs, divalproex result in significant improvement in headache characteristics; however, this was not true for Dysport. Divalproex was significantly superior to Dysport in terms of frequency and intensity in patients with episodic migraine.

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