Intravenous Valproate versus Subcutaneous Sumatriptan in Acute Migraine Attack

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Abstract- Migraine is a common and incapacitating neurologic disorder manifesting with episodic moderate to a severe headache and other symptoms such as photophobia, phonophobia, nausea, and vomiting. Triptans and ergot compounds have been used as treatment options for an acute migraine headache for many years. Triptans are considered the first line of treatment in patients with moderate to a severe migraine. Although the triptans are commonly used at any time during a migraine attack; they are more efficacious when used in the early stages of a migraine. Intravenous valproic acid has been shown to be well tolerated, safe, and with rapid onset of action in patients with acute moderate to severe and even refractory migraine. Sodium valproate is a Food and Drug Administration (FDA)–approved drug for prophylaxis of a migraine with and without aura. In this study, the main goal was to compare the effectiveness of sumatriptan versus valproate in an acute migraine. A randomized clinical trial including 37 patients with an acute migraine was considered to compare the effectiveness of sumatriptan versus valproate. The patients were divided into two groups. In first group, 6 mg subcutaneous of sumatriptan and in the second group 15 mg/Kg of valproate was administered. The outcomes including pain and drug adverse effects were compared across the groups. A total of 37 patients (7 male and 30 female) were evaluated in two groups. The difference between two groups regarding sex and age was not significant (P>0.05). The mean pain scores reduced from 8.3 to 4.7 and from 8.3 to 2.2 after one hour of treatment in sumatriptan and valproate groups, respectively. Response to treatment in valproate group was faster and more effective than sumatriptan group (P<0.05).The results indicated that valproate was more effective and with the faster response in patients with an acute migraine in comparison with sumatriptan without any recurrence and remarkable side effects.

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Keywords: Migraine; Sumatriptan; Sodium valproate

Introduction

A migraine is one of the most common types of chronic pain. A migraine usually presents with episodic moderate to a severe headache and other symptoms such as photophobia, phonophobia, nausea, and vomiting (1,2). Sleep disorders, stress, trauma, smoking, positive familial history, and some foods are effective in initiation or aggravation of a migraine (3-8). Common status and deep impact on daily life are a common cause of clinical attention in migraine patients (9,10). Triptans and ergot compounds have been used as treatment options for an acute migraine headache for many years. Triptans are considered the first line of the treatment in patients with moderate to a severe migraine. Although the triptans are commonly used at any time during a migraine attack; they are more efficacious when used in the early stages of a migraine and obviously their effects are less when a headache is established. In contrast, sodium valproate has the advantage that affects even the headache is established. Intravenous valproic acid has been shown to be well tolerated, safe, and with rapid onset of action in patients with acute moderate to severe and even refractory migraine. Sodium valproate is a Food and Drug Administration (FDA)–approved drug for prophylaxis of a migraine with and without aura. This drug has not been approved for abortive therapy so far. This study was performed to compare the effectiveness of valproate versus sumatriptan in an acute migraine.

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Materials and Methods

A total of 44 patients with an acute migraine were enrolled in an open-label randomized clinical trial. All the participants signed the informed consent form. The study was approved by Local Medical Ethics Committee, and the Helsinki Declaration was respected all over the study (code: 91/D/130/2126). Inclusion criteria were a negative history of co-morbid diseases such as hypertension, coronary artery disease, liver disease, kidney disease, headaches other than a migraine, migraine with aura, and pregnant patients. Patients who were using oral valproate, sumatriptan, ergotamine, injection analgesics, Mono Amino Oxidase (MAO)-inhibitors, and Selective Serotonin Reuptake Inhibitors (SSRI), along with the patients who had hypersensitivity reaction to intravenous valproate or subcutaneous sumatriptan were excluded from this study.

Among the patients who attended to two general referral hospitals from April, 2012 to July, 2013 with acute migraine (according to ICHD2 criteria), 44 subjects aging from 20 to 60 years were enrolled in this study. They suffered from a headache for one hour on average. They were randomly assigned to receive either 6 mg of subcutaneous sumatriptan or 15 mg/Kg of intravenous valproate. The outcomes including pain severity at 0.5, 1, 2, 4, 24, and 48 hours after injection (VAS score was used to migraine severity), other concomitant symptoms such as photophobia, phonophobia etc. and drug adverse effects were compared across the groups. Time for the onset of action, duration of drug effect, and recurrence of a headache were also evaluated. In required cases, the electrocardiogram and brain Computed Tomography (CT) scan were performed. Vital signs were also recorded across the study.

Data analysis was performed among 37 patients. Seven patients out of 44 were excluded (four patients due to incomplete filling the questionnaire and three for the use of other drugs before the scheduled treatment). Data analysis was performed by SPSS (version 18.0) software [Statistical Procedures for Social Sciences; Chicago, Illinois, USA]. Chi-Square and Independent-Sample *t*- tests were used and were considered statistically significant at P values less than 0.05.

Results

Seven subjects (19%) were male, and the mean (± standard deviation) age of the patients was 37.42±9.68 (ranging from 23 to 60 years). Eighteen patients received sumatriptan, and 19 subjects underwent treatment with valproate. The male/female ratio was 4/14 and 3/16 in sumatriptan and valproate groups, respectively (P = 0.46). The mean (± standard deviation) age of the patients was 36.17±7.57 and 38.61 ± 11.41 in sumatriptan and valproate groups, respectively (P=0.45). As shown in (Table 1), the vital signs were the same between two groups (P>0.05).

The mean pain score was alike between groups at the baseline except for 0.5 and one hours after injection (Table 2).

Table 1. Vital signs in two groups

Parameter	Sumatriptan group		Valproate group		*P.* value
	Mean	Standard deviation	Mean	Standard deviation	
Systolic blood pressure	111.92	13.62	0.2	9.69	118.16
Diastolic blood pressure	73.07	12.16	0.8	9	74.16
Pulse rate	81.76	4.83	0.63	5.29	82.75
Body temperature	36.98	0.31	0.54	0.29	36.90

Table 2. Pain score in two groups (VAS score)

Pain measurement interval	Sumatriptan group		Valproate group		*P.* value
	Mean	Standard deviation	Mean	Standard deviation	
Before Treatment	0.84	1.10	8.31	1.19	8.38
After 0.5 hour	0.001	3.35	3.31	2.35	6.83
After 1 hour	0.023	3.03	2.26	3.25	4.72
After 2 hours	0.30	2.91	2.15	2.91	3.16
After 4 hours	0.99	2.94	2.10	2.76	2.11
After 24 hours	0.68	2.68	1.68	2.79	2.05
After 48 hours	0.46	2.38	1.31	2.83	1.94

The concomitant symptoms were similar at baseline, but responded better to the treatment after 0.5 and one hours and were alleviated after 0.5 and one hours (Table 3 - $P<0.05$). The most difference (decrease of pain score) in the mean of both groups was related to the difference between 0.5 and 1 hour (Table 4). Lack of response was seen in three and two patients in sumatriptan and valproate groups, respectively ($P=0.15$). Only two patients in sumatriptan group had a recurrence ($P=0.15$). The mean (± standard deviation) effect onset time was 70.00 ± 60.11 minutes and 22.67± 18.68 minutes in sumatriptan and valproate groups, respectively *(*$P=0.04$). No drug adverse effects were seen in both groups.

Table 3. Frequency of concomitant symptoms

Pain M. I.	Symptoms	Sumatriptan group	Valproate group	*P.* value
Before treatment	Photophobia	12 (67%)	11 (58%)	0.8
	Phonophobia	12 (67%)	11 (58%)	0.5
	Nausea	18 (100%)	12 (63%)	0.004
	Vomiting	14 (78%)	1 (5%)	0.1
After 0.5 hour	Photophobia	8 (44%)	0	0.005
	Phonophobia	9 (50%)	0	0.001
	Nausea	17 (94%)	0	0.001
	Vomiting	13 (72%)	0	0.001
After 1 hour	Photophobia	5 (28%)	0	0.01
	Phonophobia	6 (33%)	0	0.006
	Nausea	12	0	0.001
	Vomiting	8	0	0.001

Table 4. Difference (decrease) of the pain score in two groups

Pain measurement interval	Sumatriptan group			Valproate group		
	P. Value	S. D.	Mean	*P.* value	S. D.	Mean
Before treatment and after 0.5 hour	0.001	3.75	5.00	0.01	2.45	1.55
After 0.5 hour and after 1 hour	0.004	2.17	1.05	0.004	2.65	2.11
After 1 hour and ater 2 hour	0.016	1.10	0.10	0.016	2.45	1.55
After 2 hours and after 4 hour	0.02	0.22	0.05	0.23	1.79	1.05
After 4 hours and after 24 hour	0.30	1.26	0.42	0.33	0.23	0.05
After 24 hours and after 48 hour	0.30	1.60	0.36	0.33	0.47	0.11

Discussion

The disabling pain of migraine attack is the leading cause of the need to treatment. Sometimes the severity of a headache especially when episodes are frequent may interfere with daily activity and result in some emotional problems for patients. Decreased self-esteem and cognitive problems are common consequences. Consequently, the treatment of the disease is necessary. In this study, the efficacy of sumatriptan and valproate were compared in patients with an acute migraine. In previous studies as well as our study, the migraine prevalence was more common in women (11). The mean age of the patients was 37 years showing the patients were mainly young adults.

We could match the age and the sex across the groups to increase the reliability of the results. In both groups, the pain score were reduced after treatment with a significant difference in before and after treatment phases and also up to four hours. The pain score showed more reduction with the faster response in valproate group compared to sumatriptan. The most decrease in pain score in sumatriptan group was after one hour with a mean reduction of 2.11 and it was after 0.5 hours with a mean reduction of 5 in a score of valproate group. Lack of therapeutic response was more common in sumatriptan group. The mean onset time was significantly shorter in the valproate group. Also, only two patients had recurrence both in sumatriptan group. Interestingly no therapeutic adverse effects were seen.

Most studies have shown similar results. Valproate has been reported to be rapid onset potent anti-migraine medication in previous studies (11-16). Bakhshayesh *et al*,. compared valproate, sumatriptan, and metoclopramide for an acute migraine and it was seen that valproate had more efficacies in comparison with two other drugs (17). Pain severity reduction was seen in 53% and 23% in valproate and sumatriptan groups, respectively in their study. However, the contributing percents were 87% and 50% in a current study showing

better outcomes in the current investigation.

Dizziness, mood alterations, blurred vision, abnormal eye movements, diplopia, flutter in visual field, increased epileptic attacks, abnormal bruise or bleeding, lack of appetite, nausea and vomiting, and severe abdominal pain are among most common drug adverse effects due to valproate use. However, this study and the report by Bakhshayesh *et al*., showed none of them in patients. Valproate had a good safety in the present study. None of the patients in both groups were excluded due to discontinuation of drugs for experiencing side effects in this study.

Photophobia and phonophobia were the most common accompanying symptoms that showed a good response to valproate and were alleviated after half an hour. However, in sumatriptan group these symptoms were not alleviated as valproate group and remained in some amounts. The study by Yurekli *et al*., inversely reported that general pain was not significantly reduced in patients who used valproate (18). These different results may be due to selection differences between studies or various used designs or even different efficacies due to the use of drugs made by different companies. It is better to perform similar studies with a similar design, study population and drugs preparations to obtain more definite and probably congruent results.

One of the main restraints in this study was small sample size that was relatively seen in other studies and may decrease the ability to the generalization of results. Also the lack of a control group reduced our ability to rule of the role of spontaneous improvement in some cases. Measurement of a placebo effect or even psychological impacts due to the use of injection drugs was also not possible. Accordingly, controlled larger multi-center studies may help for determination of most effective anti-migraine drugs.

In conclusion, valproate is more effective and has a faster response in patients with acute migraine attack in comparison with sumatriptan. No remarkable side effects are seen in the patients but two patients in sumatriptan group had a recurrence.

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