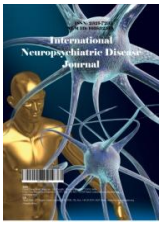

International Neuropsychiatric Disease Journal

14(3): 22-30, 2020; Article no.INDJ.61139
ISSN: 2321-7235, NLM ID: 101632319

Sodium Valproate versus Propranolol in Chronic Migraine Prophylaxis

Hossam Egila[1*], Zeinab El-Mahdy[1], Ahmed Azab[1], Mohammad Abu-Hegazy[1] and Ayman Abdel-Naby[1]

[1]Mansoura Faculty of Medicine, Mansoura University, Neurology Department, El Gomhurea St-33155, EL Mansoura, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Author ZEM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors HE, AA, MAH and AAN managed the analyses of the study. Author HE managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/INDJ/2020/v14i330130
Editor(s):
(1) Dr. Manabu Makinodan, Nara Medical University, Japan.
Reviewers:
(1) Patrick Rutendo Matowa, University of Zimbabwe, Zimbabwe.
(2) Geovane Aparecido Ramos da Silva, State University of Maringá, Brazil.
(3) Zahra Talebi, The Ohio State University, USA.
Complete Peer review History: http://www.sdiarticle4.com/review-history/61139

Original Research Article

Received 12 July 2020
Accepted 18 September 2020
Published 02 October 2020

ABSTRACT

Background: There is a need for effective, well tolerated and affordable drug for chronic migraine prophylaxis in low socioeconomic countries.
Objective: To study the efficacy and safety of propranolol and sodium valproate (a food and drug administration approved and widely used treatment for prevention of migraine) as a prophylactic treatment in chronic migraine (CM) patients and to compare their efficacy and safety to each other.
Methods: In this single center, open labeled clinical trial, 40 patients with CM were subdivided into two group: group 1 (n=20) treated with propranolol and group 2 (n=20) treated with sodium valproate. Patients maintained headache diaries over a 1-month baseline period and a 6- month active study period. The evaluation of the treatment was done after 3 and 6 months of the initiation of the treatment. The efficacy measures were evaluation of monthly attacks frequency and attacks severity using VAS of pain (visual analogue scale. Disability and impact of migraine were evaluated using Migraine assessment disability scale (MIDAS) and Headache Impact Test (HIT-6). Throughout the study, patients were monitored for any symptoms or signs of adverse effects.

**Corresponding author: E-mail: drhosamegila@gmail.com;*

Results: Of 40 patients participated in this study (mean age, 33.48; females 72.5%). At the 6th month, the study was completed by 27 patients (propranolol; n=14 and sodium valproate; n=13). Between 55 and 62% of both groups reported more than 50% reduction in monthly attacks frequency. In both groups, there was significant reduction of VAS of pain scores. Both groups showed significant improvement of HIT-6 and MIDAS scores. Before the start of treatment, 85% to 100% of patients in both groups had severe MIDAS and HIT-6 scores. At the end of the study, only 35.7% of propranolol group and 30.8 of sodium valproate group showed severe MIDAS scores and 50% of propranolol group and 40% of sodium valproate group reported severe HIT-6 scores. 55% (n=11) of patients in propranolol reported AEs related to treatment compared to 75% (n=15) in the sodium valproate group. A higher proportion of patients discontinued the treatment because of AEs in Na valproate group compared to sodium valproate group with no statistically significant difference in between (20% vs. 5%, respectively).
Conclusions: Propranolol and sodium valproate demonstrated similar efficacy and tolerability in the prophylactic treatment of CM.

Keywords: Chronic migraine; migraine prophylaxis; propranolol; valproate; headache; prophylaxis.

1. INTRODUCTION

Among the causes of chronic daily headache, chronic migraine (CM) is considered the most common cause seen by the headache specialists. Its prevalence is about 2% worldwide and it is two to six folds more prevalent in females than in males [1]. Patients with CM have headache attacks at least 15 days per month, of which at least 8 headache days per month meet diagnostic criteria of migraine or respond to migraine specific treatment for more than 3 month [2].

Each year, about 3% of episodic migraine (EM) patients transformed to CM [1]. CM is associated with significant disability on patient's life, functional impairment and reduced health-related quality of life (HRQoL) [3]. Generally, prophylactic medication can be given as soon as the diagnosis of CM is established. The main goal in the treatment of CM is to reduce its impact on patients' lives. Therefore, it is necessary to keep migraine attacks fewer, shorter and less-impairing as possible [4].

Studies on prophylactic treatment of CM are not common because most clinical studies focused on EM. Examples of Studied drugs in patients with CM specifically are: Valproate [5], amitriptyline [6], gabapentin [7], topiramate [7,8,9], Propranolol [10], atenolol [11] and BoNT-A [12].

Propranolol is one of the most widely prescribed beta blocker for migraine prophylaxis [13]. It has been prescribed for migraine prophylaxis since 1966, when Rabkin et al. accidentally discovered its efficacy in migraine in their patients who were being treated for angina pectoris [14]. It has the US Food and Drug Administration (FDA) approval for prophylactic treatment of EM [15]. It has been investigated in few studies for CM prevention. Stovener et al. reported that propranolol 160 mg and candesartan 16 mg are effective for chronic migraine prevention [16]. Study done by Domingues et al. using it as single agent or in combination with nortriptyline reported that there was no significant difference regarding its effectiveness between using it as single agent or in combination [10].

Sodium valproate is an anticonvulsant drug which has been used broadly in migraine prophylactic therapy. Its potential effect was investigated by Sorensen for migraine prophylaxis in 1988 [17]. After that, multiple clinical trials have been published which reported that Its use decreases the frequency and severity of migraine attacks [18]. Valproate is FDA approved for EM Prophylaxis [19]. There are few studies specifically evaluate the efficacy of sodium valproate in chronic migraine [20]. Sodium valproate was studied in a small randomized placebo controlled clinical trial in which 17 patients with CM received 500 mg sodium valproate twice daily, whereas 12 received placebo. There was significant improvement in frequency and severity in the group treated with sodium valproate.

Propranolol and sodium valproate are widely used in Egypt for migraine prophylaxis because of their availability and affordability and they showed great efficacy either as a single agents or in combinations but unfortunately, there are no published studies in Egypt about their effectiveness. Therefore, we planned this study to evaluate the effectiveness and tolerability of

propranolol and sodium valproate in CM as monotherapy and to compare their effectiveness and safety to each other.

2. METHODS

2.1 Study Design

This was open-labeled single-center prospective study which was carried out at Mansoura university hospitals, outpatient clinics of Neurology Department. It was conducted from March 2016 to November 2018, including a screening period of 2 months, a base-line period of 1 month, followed by 6 months treatment cycle.

2.2 Patient Characteristics

2.2.1 Inclusion criteria

The study included male and female subjects of any race between the ages of 25 and 55 years who were diagnosed with CM (CM is defined as having 15 attacks or more per month, at least 8 of which have migrainous features for at least 3 months). Patients were required to understand the requirements of the study, completing questionnaires and maintaining headache diaries.

2.2.2 Exclusion criteria

Patients were excluded if they had any other headache disorders outside of the criteria outlined above, failure of adequate trials of other preventative agents; past trials of propranolol or valproate use; Patients with contraindications to propranolol or valproate; analgesic use of more than 15 days per month; Female subjects, who were pregnant, breast feeding, or planning to become pregnant during the time frame of the study and finally Subjects with recent evidence of alcohol/drug abuse.

2.3 Treatment Protocol and Schedule

At the screening period, all potential participants were examined physically and neurologically. Laboratory and radiological investigations had been done to all of them and any patient with structural brain lesion and/or laboratory abnormalities was excluded. 40 patients were divided randomly into two groups (20 patients in each group). The first group had been treated with propranolol; the second group had been treated with Sodium valproate. All patients had a baseline period, the length of this period was established as 4 weeks to obtain a mean headache frequency for a month in order to make sure of the actual attack frequency and its severity and allowing the participants to get used to maintain headache diaries. During this period patients' migraine prophylactic drugs were tapered and then stopped 1 week prior to the start of the actual treatment phase. Abortive migraine medications were allowed as needed. Following the baseline period, treatment was initiated at day 0. The treatment efficacy evaluation was done after 3 and 6 months from day 0. Propranolol dosing was initiated at 40 mg per day then escalated to 160 mg per day over 2 weeks and the same dose was continued till the end of the study. Sodium valproate was administered at dose of 250 mg per day then was titrated to 1000 mg per day over 2 weeks and was continued to the end of the study.

2.4 Outcome Measures

Efficacy measures were reduction in headache frequency per month and reduction of headache severity using visual analogue scale of pain (VAS). It is 10 points scale at which "0 point" indicates no pain and "10 point" indicates the most severe pain [21]. All of these outcomes were determined by patients' recorded data in the headache Diaries. Other measures used to evaluate the reduction of migraine impact on patients' life were headache impact test (HIT-6) and migraine disability assessment scale (MIDAS). HIT-6 is designed to assess the impact of headache on patient's life for the past month. It is formed of six questions: Pain, role functioning, social functioning, energy or fatigue, cognition, and emotional distress [22]. The MIDAS was developed to measure headache related disability in 3 domains: (school/work), (house-hold/work) and (family, social, or leisure activities). The disability is measured by the total number of days of activity limitations due to migraine in the past 3 months [23].

2.5 Safety Assessments

Throughout the study, patients were monitored for any symptoms or signs of adverse effects (AEs). AEs for each patient were documented in details in each follow up visit and patients were allowed to report any annoying side effects outside the scheduled visits.

2.6 Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0.

Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the 0.05 level and all tests were 2 tailed. Chi-square test (was used to compare categorical variables between different groups). Student-t test was used for parametric quantitative variables, to compare between two studied groups. Mann Whitney test was used for non parametric quantitative variables, to compare between two studied groups.

3. RESULTS

3.1 Socio-Demographic Data and Initial Characteristics

A total of 40 patients (propranolol, n = 20; sodium valproate, n = 20) were recruited; the mean age was 33.48 years, 72.5% of them were females. At month 6, our study was completed by 27 patients (propranolol; n=14 and sodium valproate; n=13). The causes of discontinuation were because of side effects, loss of efficacy or loss of follow up. The two groups were mutually matched; there were no statistically significant differences between them with regard to socio-demographic data and initial characteristics and this matching between them enabled us to have a valid comparative statistical analysis (Table 1).

3.2 Efficacy Measures

3.2.1 Reduction in monthly attacks frequency

The group treated with propranolol showed significant reductions in the monthly headache frequency at month 3 (-7 (3.0-17.0), p<0.001) and at month 6 (-5 (0.0-18.0), P=0.001). Treatment with sodium valproate also significantly reduced the monthly attacks frequency at 3rd month (-7 (3.0-18.0), P<0.001) and at 6th month (0.0-20.0), P2=0.001) (Table 2). Lack of significance between the two groups was observed for 3rd month and 6 months (p=0.70 and p=0.81 respectively (Table 3). More than 50% reduction in monthly attacks frequency was not significant different between the two groups. Propranolol group showed 56.25% and 57.14 for 3rd and 6th months respectively versus 62.5% and 61.53% in sodium valproate group.

3.2.2 VAS of pain

Propranolol treatment led to significant decrees of vas basal scores at both 3rd (6.0±1.0, P<0.001) and 6th month (5.15, P<0.001). Sodium valproate also resulted in significant mean

Table 1. Socio-demographics and initial clinical characteristics

	Propranolol n=20	Na valproate n=20	P value
Age/years			
Mean ± SD	34.1±10.02	34.4±9.38	p=0.92
Sex n (%)			
• Male	8 (40.0)	9 (45.0)	p=0.70
• Female	15 (75.0)	14 (70.0)	
Marital status n (%)			
• Single	6 (30.0)	8 (40)	p=0.44
• Married	14 (70.0)	11 (55)	
• Divorced	0	1 (5)	
Residency n (%)			
• Rural	7 (35.0)	8 (40)	p=0.74
• Urban	13 (65.0)	12 (60)	
Migraine duration/years Median (Min-Max)	7.5 (1.0-35.0)	6.5 (1.0-30.0)	p=0.59
Positive family history	11 (55.0)	11 (55.0)	p=1.0
Presence of aura n(%)	5 (25.0)	3 (15.0)	p=0.44
Monthly attacks frequency Median (Min-Max)	16.0 (15.0-22.0)	16.5 (15.0-24.0)	p=0.92
VAS Mean ± SD	9.32±0.75	9.0±0.92	p1=0.19
HIT-6 Mean ± SD	71.32±5.3	68.65±4.7	p1=0.07
MIDAS Median (Min-Max)	35.0 (18.0-42.0)	29.5 (18.0-46.0)	p1=0.08

Table 2. Change of monthly attack frequency and VAS scores during follow up period among propranolol and Na valproate groups

	Before therapy	3rd month	6th month	P value	Percentage of change
Propranolol group					
Attacks frequency/month Median (min-max)	16.0 (15.0-22.0)	7.0 (3.0-17.0)	5.0 (0.0-18.0)	P1<0.001* P2=0.001*	$\%_1$=56.3 $\%_2$=68.8
VAS Mean ± SD	9.32±0.75	6.0±1.0	5.15±1.8	P1<0.001* P2<0.001*	$\%_1$=35.6 $\%_2$=44.7
Na valproate group					
Attacks frequency/month Median (min-max)	16.5 (15.0-24.0)	7.0 (3.0-18.0)	6.0 (0.0-20.0)	P1<0.001* P2=0.001*	$\%_1$=57.6 $\%_2$=63.6
VAS Mean ± SD	9.0±0.92	6.13±1.5	5.0±2.7	P1<0.001* P2<0.001*	$\%_1$=31.9 $\%_2$=44.4

**Statistically significant; $\%_1$ comparison between basal scores and 3rd month; $\%_2$ comparison between basal scores and 3rd month*

changes from the baseline at month 3 (6.13±1.5, P<0.001) and at month 6 (5.0±2.7, P2<0.001) (Table 2). No significant difference was found between the 2 groups at months 3 and 6 (p=0.77 and p=0.81 respectively) (Table 3).

3.3 Disability Measures

3.3.1 Headache impact test (HIT-6)

Group treatment with propranolol showed significant mean changes from baseline in HIT-6 scores at Month 3 (-57.6±8.01, P<0.001) and month 6 (-56.62±11.27, P2<0.001). Sodium valproate treatment also resulted in significant mean reduction in comparison to basal scores for 3rd month (57.0±8.82, P<0.001) and for 6th month (55.0±12.38, P<0.001) (Table 4). There was no statistically significant difference in between the groups for 3rd and 6th months (p=0.77 and p=0.56 respectively) (Table 5). At baseline, 100% of both propranolol and sodium valproate groups reported severe HIT-6 scores (>20). At 6 month only 50% of propranolol group and 40% of sodium valproate group reported severe HIT-6 scores with no significant difference between them (p=0.74).

3.3.2 Migraine Disability Assessment Scale (MIDAS)

Statistically significant changes from basal MIDAS total scores occurred in the propranolol group at 3rd month (-13.0 (6.0-32.0), p<0.001) and 6th month (-11.0 (2.0-36.0) P=0.001). In the sodium valproate group, there were significant reductions from baseline MIDAS total scores at month 3 (-15 (6.0-36.0), P<0.001) and at month 6 (-13.0 (3.0-40.0), P=0.001) (Table 4). The reductions in MIDAS scores was not significantly different between the two groups at any time point (p=0.44 for 3rd month and p=0.49 for 6th month) (Table 5). Before the start of treatment, 85% of patients in both groups had severe MIDAS scores. At the end of the study, 35.7% of propranolol group and 30.8 of sodium valproate group showed severe scores with no significant difference between them (p=0.78).

Table 3. Comparison of attacks frequency attacks severity distribution between studied groups

	Propranolol	Sodium valproate	P value
Attacks frequency/month median(min-max)			
Before Therapy	16.0 (15.0-22.0)	16.5 (15.0-24.0)	p1=0.92
3rd month	7.0 (3.0-17.0)	7.0 (3.0-18.0)	p1=0.70
6th month	5.0 (0.0-18.0)	6.0 (0.0-20.0)	p1=0.81
VAS Mean ± SD			
Before Therapy	9.32±0.75	9.0±0.92	p1=0.19
3rd month	6.0±1.0	6.13±1.5	p1=0.77
6th month	5.15±1.8	5.0±2.7	p1=0.81

Table 4. Changes of HIT-6 & MIDAS scores among the studied groups

	Before therapy	3rd month	6th month	P value	Percent of change
Propranolol group					
HIT-6	71.32±5.3	57.6±8.01	56.62±11.27	P1<0.001*	$\%_1$=19.2
Mean ± SD				P2<0.001*	$\%_2$=20.6
MIDAS Median	35.0 (18.0-42.0)	13.0 (6.0-	11.0 (2.0-	P1<0.001*	$\%_1$=62.9
(min-max)		32.0)	36.0)	P2=0.001*	$\%_2$=68.6
Sodium valproate group					
HIT-6	68.65±4.7	57.0±8.82	55.0±12.38	P1<0.001*	$\%_1$=16.9
Mean ± SD				P2<0.001*	$\%_2$=19.9
MIDAS Median	29.5	15.0	13.0	P1<0.001*	$\%_1$=49.2
(min-max)	(18.0-46.0)	(6.0-36.0)	(3.0-40.0)	P2=0.001*	$\%_2$=55.9

**Statistically significant, $\%_1$ comparison between basal scores and 3rd month, $\%_2$ comparison between basal scores and 3rd month*

3.3.3 Safety and tolerability assessment

Numerically greater AEs were observed in sodium valproate group versus Propranolol group, however this difference between groups didn't reach statistically significant difference (p=0.18). 55% (n=11) of patients in propranolol reported AEs related to treatment compared to 75% (n=15) in the sodium valproate group. The most frequent AEs in propranolol group were hypotension (30%), fatigue (20%) and cold extremeties and bradycardia (15%) (Table 6), while the most frequent AEs with sodium valproate treatment were dry mouth and nausea (45%), decreased appetite (40%) and smonelence (35%) (Table 6, 7). A greater proportion of patients discontinued the treatment because of AEs in both groups with no statistically significant difference (20% vs. 16.7%, respectively; P = 0.34.

Table 5. Comparison of HIT-6 and MIDAS scores between the studied groups

	Propranolol	Sodium valproate	P value
HIT-6 Mean ± SD			
Before Therapy	71.32±5.3	68.65±4.7	p1=0.07
3rd month	57.6±8.01	57.0±8.82	p1=0.77
6th month	56.62±11.27	55.0±12.38	p1=0.56
MIDAS median (min-max)			
Before Therapy	35.0 (18.0-42.0)	29.5(18.0-46.0)	p1=0.08
3rd month	13.0 (6.0-32.0)	15.0 (6.0-36.0)	p1=0.44
6th month	11.0 (2.0-36.0)	13.0 (3.0-40.0)	p1=0.49

Table 6. Side effects frequency among propranolol and sodium valproate group

Side effect*	Propranolol group n=20 (%)	Side effect*	Na Valproate group n=20 (%)
Somnolence	1 (5)	Somnolence	7(35)
Fatigue	4(20)	Fatigue	2(10)
Weight gain	1(5)	Weight gain	6(30)
Diarrhea	1(5)	Diarrhea	2(10)
Nightmares	1(5)	Increased appetite	8(40)
Difficulty sleeping	2(10)	Dry mouth & nausea	9(45)
Dizziness	1(5)	Abdominal pain, stomatitis	6(30)
Irritability	1(5)	Parathesia	3(15)
Hypotension	6(30)	Memory disturbance	5(25)
Bradycardia	3(15)	Tremors	4(20)
Cold extremities	3(15)	Vertigo	3(15)
		Anxiety	3(15)
		Blurred vision	3(15)
		Hair loss	5(25)

**Categories are not mutually exclusive*

Table 7. Comparison of side effect frequency between propranolol and sodium valproate group

Side effects	Propranolol n(%)	Na valproate n(%)	Test of significance
Present	11(55)	15(75)	χ2=3.11
Absent	9(45)	5(25)	p=0.18

4. DISCUSSION

Chronic migraine (CM) is a complex neurological disorder. It is recognized as a complication of episodic migraine (EM). Although it is less common than EM, it is substantially more disabling [24,25]. Pharmacological treatment of chronic migraine is considered a major challenge. The major targets of preventive treatment are to reduced frequency and severity of migraine headaches, and to improve the quality of life [26]. Certain antepileptic drugs, beta blockers, calcium channel blockers and tricyclic antidepressants are considered the first line for prophylactic CM treatment, and many other drugs are considered second and third line options. To date, OnabotulinumtoxinA (BoNT-A) injection is the only FDA approved drug for CM prophylaxis. A search in the literature, including EM and CM in both adults and children trials, revealed that propranolol was effective in producing more than 50% reduction in headache attacks frequency in at least 50% of patients in different studies [27,14,28,10,29]. Sodium valproate was effective in producing more than 50% reduction in migraine attack frequency in at least 48% of patients in different studies including EM, CM trials in adults and children [5,14,29,30,31].

To our knowledge, this is one of the first published comparative studies that specifically compares the efficacy and tolerability of propranolol to sodium valproate in CM adult patients. The findings of this study reveal that treatment with propranolol and sodium valproate showed significant improvement from the baseline.

More than 55% of Patients treated with propranolol experienced more than 50% improvement in attacks frequency. This improvement is in accordance with a study done by Domingues et al. [10] which invloved both EM and CM and in another study at which long acting propranolol was used in EM prophylaxis [32]. Also patients treated with propranolol experienced significant reduction in attacks severity, migraine impact and disability (VAS, HIT-6 and MIDAS scores).

Sodium valproate treatment resulted in significant improvement of monthly attacks frequency and significant improvement of attacks severity (VAS scores), this improvements are consistent with those found in another clinical trial which involved CM patients and other patients with other causes of chronic daily headache [5]. Sodium valproate treatment also resulted in significant improvement of patients' quality of life, there were significant reductions in migraine disability and impact, this is in agreement with a study done by Blumenfled et al. [32] at which treatment with divalproex sodium was compared to BoNT-A injection in both patients with EM and CM.

There were no significant differences between the two groups throughout the entire duration of the study regarding efficacy measures using monthly attacks frequency and Vas of pain. This is consistent with the results of Kaniecki, R.G. [28] study taking in consideration that the comparison between the two drugs in his study was in patients suffering from migraine without aura and the maximum headache frequency was 15 attacks per month. Another study done by Asharfi et al. showed that there was no significant difference in frequency, severity, duration and showing better response to abortive medications, this study was done in pediatric age group with mean monthly attack frequency of 7.8 and 7.9 for sodium valproate and propranolol respectively [14]. In study of Bidabadi and Mashoup [29] which was in pediatric age group with mean attack frequency of 13.86±2.11 in propranolol group and 13.23±2.43 in sodium valproate group, it was reported that there was no significant differences between the two groups in all evaluated parameters such as attacks duration, severity and Reduction of baseline headache frequency by >50% except for the mean headache frequency per month which was lower in propranolol group than with sodium valproate group. Our study demonstrates no significant differences between the two groups of many quality of life factors; this was evaluated by Midas and HIT-6.

In this study, treatment with sodium valproate and propranolol in CM patients were well

tolerated and safe. Although propranolol and sodium valproate can cause side effects, none of these side effects were serious. There were no statistically significant differences between the two groups regarding the frequency of side effects taking in the account that A relatively higher proportion of patients in sodium valproate group (75%) reported side effects in comparison to the propranolol group (55%), but this didn't result in a statistically significant difference between the groups. This is consistent with the results of the previous studies [28,29]. The discontinuation rate due to side effects was 5% and 20% for propranolol and sodium valproate groups respectively, this is in agreement with the study done by Kaniecki, R.G. [28] who reported that the discontiuntation rate due to side effects was 3% and 11% for propranolol and divalproex sodium groups respectively and in contrast with study of Bidabbadi and Mashouf [29] who reported that no one discontinued the study because of side effects. Our study has limitations, one major limitation is that the absence of a control group. Another limitation was that the attacks duration was not evaluated because patients were not able to completely withdraw the acute treatment.

5. CONCLUSION

Propranolol and sodium valproate treatments demonstrated significant efficacy in patients with CM, more than 50% of patients in each group showed more than 50% reduction in monthly attacks frequency. Both drugs were well tolerated and resulted in significant improvement of quality of life. There no significant differences between these two drugs in all evaluated parameters and safety and tolerability measures.

CONSENT AND ETHICAL APPROVAL

Prior to the initiation of the study, all procedures was reviewed by ethical and research committee, Mansoura University. Written informed consent was obtained from all participants, they were informed about the nature and objectives of the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Aurora Sheena K, Mitchell F. Brin. Chronic migraine: An update on physiology, imaging and the mechanism of action of two available pharmacologic therapies. Headache. 2017;57(1):109–25.
2. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd Edition, Beta Version. Cephalagia; 2013.
3. Diener HC, Dodick DW, Aurora SK, Turkel CC, et al. Onabotulinumtoxin A for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010;30(7):804–14.
4. Escher Claus M, Lejla Paracka, Dirk Dressler, Katja Kollewe. Botulinum toxin in the management of chronic migraine: Clinical evidence and experience. Therapeutic Advances in Neurological Disorders. 2017;10(2):127–35.
5. Yurekli, et al. The effect of sodium valproate on chronic daily headache and its subgroups. The Journal of Headache and Pain. 2008;9(1):37–41.
6. Couch James R. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache. 2011;51(1):33–51.
7. Spira PJ, Beran RG, Australian Gabapentin Chronic Daily Headache Group. Gabapentin in the prophylaxis of chronic daily headache a randomized, placebo-controlled study. Neurology. 2003;61(12):1753–1759.
8. Silvestrini M, et al. Topiramate in the treatment of chronic migraine. Cephalalgia: An International Journal of Headache. 2003;23(8):820–24.
9. Diener HC, et al. Topiramate reduces headache days in chronic migraine: A randomized, double-blind, placebo-controlled study. Cephalalgia. 2007;27(7):814–23.
10. Domingues, Renan B, et al. A double-blind randomized controlled trial of low doses of propranolol, nortriptyline and the combination of propranolol and nortriptyline for the preventive treatment of migraine. Arquivos de Neuro-Psiquiatria. 2009;67(4):973–77.
11. Edvardsson Bengt. Atenolol in the prophylaxis of chronic migraine: A 3-month open-label study. SpringerPlus. 2013;2(1):1–5.
12. Diener HC, Dodick DW, Aurora SK, Turkel CC. Onabotulinumtoxin A for treatment of chronic migraine: Results from placebo-

controlled phase of the PREEMPT 2 trial. 2010;30(7):804–14.
13. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. The Cochrane Library. 2004;2.
14. Ashrafi MR, Shabanian R, Zamani GR, Mahfelati F. Sodium valproate versus propranolol in paediatric migraine prophylaxis. European Journal of Paediatric Neurology. 2005;9(5):333–38.
15. Shapiro Robert E. Preventive treatment of migraine. Headache: The Journal of Head and Face Pain. 2012;52(s2):65–69.
16. Stovner Lars J, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014;34(7):523–32.
17. Sorenson KV. Valproate: A new drug in migraine prophylaxis. Acta Neurologica Scandinavica. 1988;78:346–48.
18. Rahimdel, Abolghasem, et al. Effectiveness of vitamin B2 versus sodium valproate in migraine prophylaxis: A randomized clinical trial. Electronic Physician. 2015;7(6):1344–48.
19. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: Breaking down barriers to optimal treatment and prevention. Headache: The Journal of Head and Face Pain. 2015;55((S2)):103–122.
20. Edward Justin A, Stacy Mandras. An update on the management of chronic migraine. Current Problems in Cardiology. 2016;42(12):7–38.
21. Wewers Mary Ellen, Nancy K. Lowe. A critical review of visual analogue scales in the measurement of clinical phenomena. Research in Nursing & Health. 1990;13(4):227–36.
22. Dowson AJ. Assessing the impact of migraine. Current Medical Research and Opinion 2001;17(4):298–309.
23. Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: The Migraine Disability Assessment (MIDAS) questionnaire. Headache. 2001;41(9):854–61.
24. Roceanu A, Antochi F, Bajenaru O. Chronic migraine–New treatment options. Mædica Roceanu Antochi Bajenaru. 2014;9(4):401–4.
25. Barbanti P, et al. Rationale for use of onabotulinum toxin A (BOTOX) in chronic migraine. Neurological Sciences. 2015;36(1):29–32.
26. Fenstermacher N, Levin M, Ward T. Pharmacological prevention of migraine. Bmj. 2011;342:d543.
27. Holroyd Kenneth A, Donald B. Penzien, Gary E. Cordingley. Propranolol in the management of recurrent migraine: A metaanalytic review. Headache: The Journal of Head and Face Pain. 1991;31(5):333–40.
28. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. Arch Neurol. 1997;54(9):1141–45.
29. Bidabadi Elham, Mehryar Mashouf. A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Pediatric Drugs. 2010;12(4):269–75.
30. Linde Mattias, Wim M. Mulleners, Edward P. Chronicle, Douglas C. McCrory. Valproate (Valproic Acid or Sodium Valproate or a Combination of the Two) for the prophylaxis of episodic migraine in adults. Cochrane Database of Systematic Reviews. 2013;6.
31. Pradalier A, et al. Long-acting propranolol in migraine prophylaxis: Results of a double-blind, placebo-controlled study. Cephalalgia : An International Journal of Headache 1989;9(4):247–53.
32. Blumenfeld, et al. Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache. 2008;48(2):210–20.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/61139