

Dual versus Monotherapy in the Prophylaxis of Acute and Chronic Migraine

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ABSTRACT

Background: Migraine, a primary headache disorder, is a debilitating condition with reduced productivity, increased disability, and a very high economic burden. The present study aimed to individualize the treatment protocols for episodic and chronic migraine in order to reduce the duration, frequency, and severity of attacks, as well as the disability associated with migraine by comparing monotherapy and dual therapy. **Materials and Methods:** We conducted a prospective observational study between February 2019 and July 2021. Patients were diagnosed with migraine based on simplified diagnostic criteria. Episodic migraine was present in 62% and chronic migraine in 38% of cases. Disability due to headache was assessed using the Migraine Disability Assessment Score (MIDAS) questionnaire. Prophylactic therapy was individualized, with 210 patients receiving monotherapy (propranolol, flunarizine, or valproic acid) and 190 patients receiving dual therapy (propranolol and flunarizine, or valproic acid and flunarizine). Disability at baseline was graded from I to IV, and improvement after treatment was graded as no recurrence of headache, grade I, grade II, and grade III. **Results:** After 2–3 months of therapy, we observed significant improvement in the form of reduction in the frequency of attacks and reduction of disability. Patients with grade II disability who received dual therapy showed 100% improvement with no recurrence of headaches. Treatment with valproic acid resulted in no recurrence in 100% of patients with grade I and 85.7% of patients with grade II disability scores. Significant improvement was observed in all grades of disability with dual therapy. **Conclusion:** Dual prophylactic therapy was more efficient than monotherapy in reducing the frequency, duration, and severity of symptoms in grade III and grade IV patients.

Keywords: Migraine Disability Assessment (MIDAS) score, monotherapy, dual therapy

INTRODUCTION

Migraine is a primary headache disorder and the second most common incapacitating and painful disorder in the world, affecting 6% of men and 15% of women.¹ The global prevalence of migraine is one in seven, and it is the seventh cause

of disability in the world.^{2,3} Results from the International Burden of Migraine Study (IBMS) show that migraine-related disability has a high economic burden.⁴ According to the International Classification of Headache Disorders, episodic migraine (EM) lasts <15 days per month, and chronic migraine (CM) lasts >15 days per month.⁵ It has been estimated that about 2.5% of individuals with EM eventually progress to CM over time.⁶

The degree of disability at baseline and the subsequent response to treatment is usually determined with the Migraine Disability Assessment Score (MIDAS), a well-validated tool in the form of a questionnaire.⁷ Management protocols involve a combination of non-pharmacological and pharmacotherapeutic interventions. The former includes lifestyle modification and avoidance of known trigger factors.^{8,9} Pharmacological therapy includes abortive medications for acute attacks and prophylactic treatment for chronic migraineurs. Prophylaxis aims to reduce the severity, frequency, and duration of the attacks, thereby reducing the disability associated with the disease. Drugs used for prophylaxis include beta blockers such as propranolol, metoprolol, and nadolol; anticonvulsants such as valproic acid and topiramate; calcium channel blockers such as flunarizine; and antidepressants such as amitriptyline, dosulepin, venlafaxine, and desvenlafaxine.^{10,11} Onabotulinum toxin A has recently been approved for migraine prophylaxis when headaches occur for more than 14 days a month. It is given every 12 weeks as multiple injections around the head and neck to try to dull future headache symptoms.¹²

The aim of this study was to explore the possibility to individualize the treatment protocols for episodic and chronic migraine in order to reduce the duration, severity, and frequency of attacks, as well as the disability associated with migraine by comparing monotherapy (propranolol, flunarizine, valproic acid) and dual therapy (propranolol and flunarizine, valproic acid and flunarizine).

MATERIALS AND METHOD

We carried out a prospective observational study between February 2019 and July 2021 on 400 patients in the outpatient neurology department of a tertiary care multispecialty teaching hospital, based on the simplified diagnostic criteria for migraine of the Headache Classification Committee of the International Headache Society, published in 2013. Written informed consent was obtained from all study participants, and the study was approved by the ethics committee of the institution where it was performed.

A standardized structured questionnaire was used to carry out the interview with regards to clinical symptom

location, severity of pain, frequency of attacks, and the quality of headache. Comorbidities and migraine triggers were also assessed. These factors are both directly and indirectly related to the overall treatment response and the benefits of prophylactic treatment in migraine patients. Furthermore, a 5-item MIDAS questionnaire was filled out to assess the grade of disability associated with the migraine. The MIDAS scale quantifies the amount of disability and reduction in activity concerning school work, household work, employment etc. Greater disabilities are associated with higher scores. Scores were graded as grade I, grade II, grade III, grade IV, and Severe disability. Two groups of patients were selected randomly: the first one received monotherapy, and the second one received dual therapy as prophylactic treatment. Patients on monotherapy were randomly divided into 3 subgroups of 70 patients each. Each subgroup was put on beta blocker propranolol 20 mg/40 mg twice daily, cerebroselective calcium channel blocker flunarizine 10 mg once daily, and valproic acid/sodium valproate 250 mg/500 mg once daily, respectively. The other group of patients was put on prophylactic dual therapy for both episodic and chronic migraine and was subdivided into 2 subgroups of 95 patients each. One subgroup received a combination of propranolol 20 mg with flunarizine 10 mg, and the other received valproic acid 250 mg with flunarizine 10 mg. Patients were assessed before and after initiating prophylactic treatment, and disability at baseline was graded from I to IV. Likewise, improvement after treatment was graded as no recurrence of headache, grade I, grade II, and grade III. After 2–3 months of therapy, we observed improvement in the form of reduction in the frequency of attacks and reduction of disability. The MIDAS questionnaire was filled out again, to assess the improvement in the disability grades compared to the baseline MIDAS score.

The data was analyzed using Statistical Package for the Social Sciences software version 22 (SPSS Inc, Chicago, IL, USA). An independent t-test was used to compare the means of the groups, and a p value of less than 0.05 was considered significant.

RESULTS

Among the 400 patients with migraine, 72 (18%) were males and 328 (72%) females. The majority of patients were in the age group of 25–35 years (28%) followed by 36–45 years (25%). Two hundred ten (52.5%) patients were put on monotherapy and 190 (47.5%) on dual therapy.

Disability scores at baseline and their improvement after monotherapy with propranolol 20 mg/40 mg are present-

TABLE 1. Baseline disability scores and improvement after treatment with monotherapy (propranolol)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Propranolol 20 mg/ 40 mg BID	Disability at baseline	Grade I	N	10	0	–		10	>0.05
			% showing improvement	100.0%	0.0%	–	–	100.0%	
		Grade II	N	10	5	2	–	17	
			% showing improvement	58.8%	29.4%	11.7%	–	100.0%	
		Grade III	N	8	12	4	–	24	
			% showing improvement	33.3%	50.0%	16.6%	–	100.0%	
		Grade IV	N	3	13	2	1	19	
			% showing improvement	15.7%	68.4%	10.5%	5.2%	100.0%	
Total	N	31	30	8	1	70			
	% showing improvement	44.28%	42.8%	11.42%	1.4	100.0%			

TABLE 2. Disability scores and improvement with monotherapy (flunarizine)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Flunarizine 10 mg	Disability at baseline	Grade I	N	10	0	0	0	10	>0.05
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
		Grade II	N	11	4	2	0	17	
			% showing improvement	64.0%	23.5%	11.76%	0.0%	100.0%	
		Grade III	N	6	15	1	2	24	
			% showing improvement	24.0%	62.5%	4.1%	8.3%	100.0%	
		Grade IV	N	3	13	2	1	19	
			% showing improvement	15.7%	78.9%	10.52%	5.2%	100.0%	
Total	N	30	32	5	3	70			
	% showing improvement	42.8%	45.7%	71%	3.3%	100.0%			

ed in Table 1. None of the patients with grade I scores had recurrence. Patients with grade II scores showed a 58.8% improvement with no recurrence. Those with grades III and IV showed little improvement. Clinical improvement after monotherapy with cerebroselective drug flunarizine 10 mg are presented in Table 2.

Prophylactic monotherapy with valproic acid 250 mg/500 mg led to a significant improvement in all grades of disability scores (Table 3). Grade I patients improved by 100%, and grade II patients showed no recurrence in 85.7% of cases. Grade III and grade IV patients improved to a disability score of grade I.

Improvement after dual therapy with propranolol and flunarizine are presented in Table 4, and the modifications of headache disability scores after dual therapy with valproic acid and flunarizine are presented in Table 5. We observed a reduction in disability scores from grade I and grade II at baseline to no recurrence of headache follow-

ing dual prophylactic therapy ($p < 0.001$). Dual therapy has also reduced the disability scores of grade III and grade IV patients.

DISCUSSION

In the current study, participants who were administered propranolol 20 mg or 40 mg twice daily as monotherapy showed improvement from baseline disability and most patients did not report any recurrence during follow-up visits. Silberstein et al. conducted a similar study in which beta blockers propranolol (20–80 mg/day), timolol (10–15 mg twice daily), and metoprolol tartrate (50–200 mg/day) were effective in the prophylaxis of migraine as monotherapy.¹³ These drugs are contraindicated in patients with bronchial asthma, congestive heart failure, dyslipidemia, and diabetes. Participants who were put on cerebroselective calcium channel blocker flunarizine as a prophylactic

TABLE 3. Disability scores and improvement with monotherapy (valproic acid)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Valproic acid 250 mg/500 mg	Disability at baseline	Grade I	N	9	0	0	0	9	>0.05
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
		Grade II	N	18	3	0	0	21	
			% showing improvement	85.7%	14.3%	0.0%	0.0%	100.0%	
		Grade III	N	4	15	1	0	20	
			% showing improvement	20%	75%	5%	0.0%	100.0%	
		Grade IV	N	1	17	1	1	20	
			% showing improvement	5%	85%	5%	5%	100.0%	
		Total	N	32	35	2	1	70	
			% showing improvement	45.7%	50%	2.8%	1.4%	100.0%	

TABLE 4. Disability scores and improvement with dual therapy (propranolol 20 mg and flunarizine 10 mg)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Propranolol 20 mg and flunarizine 10 mg	Disability at baseline	Grade I	N	30	0	0	0	30	<0.001
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
		Grade II	N	25	0	0	0	25	
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
		Grade III	N	15	5	5	0	25	
			% showing improvement	60%	20.6%	20%	0.0%	100.0%	
		Grade IV	N	10	3	2	0	15	
			% showing improvement	66%	20%	13.3%	0.0%	100.0%	
		Total	N	80	8	7	0	95	
			% showing improvement	84.4%	88.4%	7.3%	0%	100.0%	

lactic medication for both episodic and chronic migraine showed complete symptomatic relief with no recurrence in 100% of cases with grade I disability, while 64% of patients had no recurrence who had initially grade II disability scores. The results suggest that flunarizine is a better prophylactic drug, especially for patients with grade I and grade II disability scores. The possible side effects, such as sedation, weight gain, and depression, may limit its use in some patients.

According to the 2022 guideline of the Scottish Intercollegiate Guidelines Network for the pharmacological management of migraine, sodium valproate is more effective than placebo for patients with episodic migraine and provides $\geq 50\%$ reduction in headache frequency over a period of 2–3 months.¹⁴ Being a teratogenic drug, it cannot be used as a first-line migraine prophylactic in women of childbearing age. Its efficiency is comparable to flunarizine 10 mg and propranolol 20 mg/40 mg.

Our study also showed that all patients with grade I disability scores had 100% improvement, with a reduction in headache frequency. Moreover, participants with grade III disability scores improved to a grade I score in 75% of cases. Linde et al. observed that sodium valproate was more effective than placebo as a prophylactic migraine medication, with a $\geq 50\%$ reduction in headache frequency over a period of 2–8 months.¹⁵ Possible side effects of valproic acid include alopecia, tremors, liver damage, and polycystic ovarian disease in girls, which can limit its use in the prophylaxis of episodic and chronic migraine.

Participants who received dual prophylactic medication (propranolol 20 mg + flunarizine 10 mg) had a significant reduction in their disability scores, as well as a decrease in the frequency of headaches. Participants with grade III and grade IV disability scores showed significant improvement, with no recurrence of symptoms. Our study also revealed that dual therapy with valproic acid 250 mg and flunarizine

TABLE 5. Disability scores and improvement with dual therapy (valproic acid 250 mg and flunarizine 10 mg)

				Post-treatment improvement				Total	p value
				No recurrence	Grade I	Grade II	Grade III		
Valproic acid 250 mg and flunarizine 10 mg	Disability at baseline	Grade I	N	25	0	0	0	25	<0.001
			% showing improvement	100.0%	0.0%	0.0%	0.0%	100.0%	
	Grade II	N	30	0	0	0	0	30	
			% showing improvement	100%	0.0%	0.0%	0.0%	100.0%	
	Grade III	N	15	10	0	0	0	25	
			% showing improvement	60%	40.0%	0.0%	0.0%	100.0%	
	Grade IV	N	5	10	0	0	0	15	
			% showing improvement	33.3%	66.6%	0.0%	0.0%	100.0%	
	Total	N	75	20	0	0	0	95	
			% showing improvement	78.9%	21.0%	0.0%	0.0%	100.0%	

10 mg showed excellent outcomes, as patients with grade III and grade IV disability scores showed no recurrence for a period of 3 months. The continuation of dual therapy has ameliorated the symptoms of both acute and chronic migraine, and improved the quality of life to a greater extent.

CONCLUSIONS

Patient-tailored migraine treatments need to be explored by evaluating the degree of attack frequency and calculating disability scores that account for the presence of medical or psychiatric comorbidities and associated trigger factors. In this study, dual therapy showed significant improvement and more tangible prognostic results than monotherapy, especially in patients with grade III and grade IV disability scores, as it markedly decreased the severity of pain, duration of headache, and frequency of attacks. A combination treatment with valproate and flunarizine can represent a better therapeutic armamentarium to tackle the disability associated with migraine, alleviate the pain, and improve the lives of migraine patients.

CONFLICT OF INTEREST

All authors declare no potential conflicts of interest.

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