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The efficacy of combined low-doses of propranolol and flunarizine in episodic migraine

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ABSTRACT

This retrospective review is to evaluate the efficacy of a fixed combination of low doses of long - acting propranolol and flunarizine, when flunarizine mono therapy is ineffective in migraine.

Thirty- five patients (ages 21-57 years; average 36.5 years; male-female ratio, 1:4) compatible with the diagnosis of migraine without aura received an initial single evening dose of flunarizine of 10 mg for a period of 8 weeks and none of them showed change of migraine attacks per month. These patients were divided into two treatment groups - Group A received a fixed combination of 20 mg. long acting propranolol and 5mg. flunarizine and group B received a fixed combination of 40mg. long acting propranolol and 10mg. flunarizine for a period of 8 weeks, without a "drug-free" period of observation. The patients were assessed at the end of 8 weeks period for differences in attack frequency, duration and intensity compared to the baseline as well as in both the treatment groups.

Both groups showed significant reduction in the mean (±SD) of monthly migraine frequency, headache intensity, and headache duration (Wilcoxon Signed Rank test, significant at $p \leq 0.01$) when compared to baseline parameters. However, there was no significant difference in frequency, duration and severity (Mann–Whitney U test, not significant at $p \leq 0.05$) for both doses groups when compared. There was no adverse effect observed.

This study suggests that the fixed dose combination of 20 mg propranolol and 5 mg flunarizine could be a new treatment initiative, especially for patients in whom flunarizine mono therapy is ineffective in migraine prophylaxis

Key Words: Migraine prophylaxis, flunarizine, propranolol, fixed dosage combinations

Introduction

Migraine is a common and disabling health problem and the primary goals of preventive treatment are to reduce attack frequency, severity, and duration. Every patient is different and there is no 'right' prophylactic agent. The utility of flunarizine and propranolol in migraine prophylaxis are well-known. In all trials flunarizine was equally effective with the β-adrenoceptor blockers, but had a qualitatively different adverse event profile. Based on these comparative studies as well as the placebo-controlled trials (1,2), flunarizine is considered a drug of first choice in migraine prophylaxis. But in a substantial number of patients 10 to 20%, the flunarizine remains ineffective (3). The study of Pascual J et al. (4) shows that low doses of propranolol are effective in controlling serious migraine bouts in many patients (75.5%). And the study of Bassi P et al. (5) shows low doses of flunarizine are essentially effective as migraine prophylaxis while the incidence of side effects was considerably reduced in the patients treated with the lower dose. Few trials have evaluated combination of two or more drugs in the preventive treatment of migraine (6-15). The combined therapy proved to be as safe as the mono therapy. However, the optimal anti-migraine combination dosage is still unknown. This study is designed to evaluate the efficacy of a fixed combination of low doses of long-acting propranolol (LAP) and flunarizine compared with a fixed combination of classical doses of long-acting propranolol (LAP) and flunarizine, when the efficacy of flunarizine fails at the "classical" dose of 10 mg.

Materials and Methods

This retrospective, open-label study was set up at the author's private out -patient neurology clinic in remote North-East India during the period 2010 to 2015. The author identified thirty- five patients (ages 21-57 years; average 36.5 years; male-female ratio, 1:4) compatible with the diagnosis of migraine without aura according to the criteria of the Headache Classification Committee of the International Headache Society (16), who had received a fixed combination of long-acting propranolol and flunarizine for a period of 8 weeks. The inclusion criteria were: age

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over 18 years, presence of 3 or more attacks of migraine per month, and all of them currently received prophylactic medication, an initial single evening dose of flunarizine of 10 mg for a period of 8 weeks and none of them seemed to response to the prophylaxis i.e. no change of migraine attacks per month at the end of 8 weeks period. All patients had normal neurological examination. They did not show any other health problems. The exclusion criteria were any health problems other than migraine without aura or having more than 14 attacks of migraine per month. These patients were divided into two treatment groups- Group A received a fixed combination of 20mg. long- acting propranolol and 5 mg. flunarizine (low dose combination group) and group B received a fixed combination of 40 mg. long-acting propranolol and 10 mg flunarizine (classical dose combination group) for a period of 8 weeks, without a "drug-free" period of observation. All patients were informed of, consented to treatment. We reviewed each subject's: number of headache days per month, pain intensity with a numerical 0-to-10 point scale and duration of headache in hours before starting the treatment (known as the *baseline* or *pretreatment*). The author also collected the following outcome measures from the registry: number of headache days per month, pain intensity with a numerical 0-to-10 point scale and duration of headache in hours again at the end of the treatment period (*post-treatment*). Any troublesome adverse effects of drugs were investigated. The patients were assessed at the end of 8 weeks period for differences in attack frequency, duration and intensity compared to the baseline as well as in both the treatment groups.

The statistical evaluation was performed using Mann-Whitney U-test (two-tailed probabilities) for intergroup comparisons (P1) and Wilcoxon signed-ranks test (two-tailed probabilities) for intra group comparisons (P2).

Results

Thirty-five patients entered and completed the study, with 19 in group A (15 females, 4 males) with a mean age of 35.16 ± 8.57 years (range 21-52 years) and 16 in group B (13 females, 3 males) with a mean age of 38.19 ± 8.88 years (range 25-57 years). The mean Migraine duration was 10.67 ± 8.57 years (range 6 months-30 years) in group A patients and 12.16 ± 10.02 years (range 6 months - 35 years) in group B patients.

The comparative efficacy of medications between two groups of patients are summarized on Table 1.

Group A patients showed a reduction in the mean (±SD) of monthly migraine frequency from 7.21 (±3.60) to 1.52 (±1.61) episodes per month, headache intensity from 9.0 (±0.82) to 1.53(±1.50) based on the 0 to 10 points pain Scale, and headache duration from 38.11 (±23.68)

Table 1. Data at evaluation times, and intra- and inter groups comparisons

	Evaluation times	Combined propranolol LA 20 mg with Flunarizine 5 mg (n=19)	Combined propranolol LA 40 mg with Flunarizine 10mg (n=16)	P1*
Attack Frequency	Baseline (T1)	7.21±3.60(3-14)	8.19±4.00(3-14)	U:136.5,critical:92
	Month 2 (T2)	1.52±1.61(0-4)	1.44±1.46(0-4)	U:151.5,critical:92
	Change (T1-T2)	5.68±2.38(3-10)	6.75±3.00(3-11)	U;123.0,critical:92
	P2**	W-0, critical value:32	W:0, critical value:19	
Attack Duration	Baseline (T1)	38.11 ± 23.68(4-72)	34.00 ± 21.61(4-72)	U:138,critical:92
	Month 2 (T2)	2.95 ± 3.10(0-12)	4.50 ± 3.69(0-12)	U:111,critical:92
	Change (T1-T2)	34.95±22.93(3-72)	29.5±20.21(0-72)	U:132.5,critical:92
	P2**	W:0, critical value:32	W:0, critical value:15	
Attack Severity	Baseline (T1)	9.0 ± 0.82(8-10)	8.47 ± 0.64(8-10)	U:106.5,critical:92
	Month 2 (T2)	1.53 ± 1.50(0-4)	1.94 ± 1.39(0-4)	U:128.5,critical:92
	Change (T1-T2)	7.47±2.04(4-10)	6.62±1.75(4-10)	U:112.5,critical:92
	P2**	W:0, critical value:32	W:0, critical value:19	

P1: inter-group comparison; P2: Baseline and month 2 intra-group comparison.
* the result is not significant at p≤ 0.05
** the result is significant at p≤ 0.01

to 2.95 (±3.10) hours. Overall, the change in migraine attack frequency, duration and severity from baseline to end-point in group A patients was statistically significant (Wilcoxon Signed Rank test, significant at p≤ 0.01). In the group B patients, the mean (±SD) of monthly headache frequency declined from 8.19 (±4.00) to 1.44 (±1.46) per month, headache intensity lessened from 8.47 (±0.64) to 1.94 (±1.39) and headache duration decreased from 34.00 (±21.61) to 4.50 (±3.69) hours (Wilcoxon Signed Rank test, significant at p≤ 0.01). Overall, the outcome measures in the two dosage groups in the prophylaxis of migraine was essentially identical. However, there was no significant difference in frequency, duration, severity and changes from baseline to month 2 for both doses groups when compared (Mann–Whitney U test, not significant at p≤ 0.05). There was no adverse effect observed.

Discussion

In this study fixed-combination of long-acting propranolol and flunarizine used as second line therapy, when flunarizine mono therapy failed to demonstrate a satisfactory benefit. For the sake of homogeneity, the author dealt only with migraine without aura patients. This retrospective, open-label study directly compared two different fixed Dose Combinations (FDCs) of propranolol and flunarizine. In this study it is also noted that propranolol was added with flunarizine without a "drug-free" period of observation, that is without washout periods for previous medication. This was in fact study of add-on efficacy of propranolol with flunarizine. It is also to be noted that the dosages of propranolol 20 mg and 40 mg used for the prophylaxis are much lower than those commonly used as 80-160 mg daily of propranolol (17-20). This was to show whether a very low dosage combination of long-acting propranolol and flunarizine was effective or no in the prophylaxis of episodic migraine without aura. An additive effect of propranolol and flunarizine may allow for a reduction in drug dosage. In addition, propranolol and flunarizine have different mechanisms of action in the headache treatment (21). Propranolol is thought to exert its effects through its activity at 5-HT2 receptor sites (21,22). Flunarizine as a calcium channel antagonist prevent spasm of cerebral vessels by inhibiting contraction of smooth muscle (22). In the present study there was no drop out of patients and all patients remained adherence to the treatment. This adherence to the treatment may be due to once- daily schedule of low dosage drugs decreasing pill burden.

No significant differences were found in this study between the 2 groups in the baseline parameters. This fact suggests that there has been homogeneity between the two groups. The very high therapeutic gain of combination therapy used both at the "classical" dose level and at the less usual dose level in our study are an interesting finding. It is worthy to mention here that the outcome measures in the two dosage groups was essentially identical. Furthermore, the use of this fixed dose combination was well tolerated. It is likely to the positive outcome trends in patients on combination 60 mg propranolol and 10 mg flunarizine therapy in a double-blind trial (11) and combination 40 mg propranolol and 20 mg nortryptiline therapy in another double-blind trial (12). But, our study brings out the very low dose combination of 20 mg propranolol and 5 mg flunarizine has very high therapeutic gain. So, this preliminary study suggests that the fixed dose combination of 20 mg propranolol and 5 mg flunarizine could be a new treatment initiative, especially for patients in whom established flunarizine mono therapy is ineffective. Whether treatment benefit persists, increases or wanes is unknown in this study. This is a retrospective study with inherent limitations and is interpreted with caution. Due to a small group of patients in this study, the author think that only cumulative data from many studies or larger double-blind randomized controlled trials could reveal the true success rate of this fixed combined drugs.

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