Original Research Article

Comparing Efficacy of Propranolol Plus Flunarizine Combination and Valproate Monotherapy in Migraine Prophylaxis in Rural Bengal -A Randomized Control Trial

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Abstract

Migraine is second most common cause of headache which is responsible for reduction in the quality of life affects near about 15% of women and 6% of men over a period of 1 year. Affect boys and girls in similar fashion in prepubescent age group, but girls are affected more than boys after that with a rise of incident in fourth decade of life. Propranolol plus Flunarizine combination and sodium valproate are the two widely accepted therapy of migraine prevention. Head to head studies are few with these drugs and we have taken MIDAS Score with reduction of frequency and duration of migraine headache as primary and European quality of life index with EQ-VAS score for quality of life assessment, all these parameters are not included in any other one study. A randomized control trial was done at Bankura Sammilani Medical College with population from rural Bengal, data was taken and detail and appropriate statistical analysis was done with appropriate software. Both the drugs were found very much effective for migraine prophyalxis and improving quality of life. In case of EQ -5D-5L valproate was found to be more effective in improving few parameter.

Keywords :Migraine, Propranolol, Flunarizine, Valproate, Prophylaxis.

Introduction

Migraine is one type of headache, descripted as recurring syndrome of headache associated with other certain neurological dysfunction in varying admixtures. It is the second most common cause of headache, and it is most common headache related, and indeed neurologic cause of disability in the world, affects near about 15% of women and 6% of men over a period of 1 year[1]. Migraine has a one-year prevalence of 12% in the general population, it consist of 18% in case of women and 6% of men[2,3].

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Migraine has similar distribution in prepubescent boys and girls. Girls are more affected than boys and the pattern seen from the time of puberty. Peak migraine prevalence for both sexes occurs in the fourth decade of life in the time period approximately 24% of women and 7% of men have migraine[2]. QOL(Quality of Life) is the most affected parameter in migraine, feeling of well being is greatly hampered in migraine patients. Studies performed in different countries, either on individuals from the general population or on patients from headache clinics, reveal that migraine is associated with significantly lower scores on various health-related quality-of-life rating scales, regardless of age, gender, or socioeconomic status[4,5]. Propranolol is β adrenergic receptor antagonist and is nonselective ("first generation"). Beta blockers were developed primarily for control of cardiac symptoms, but it was found coincidentally that these drugs had a remarkable

effect on migraine prevention. After this chance observation was made, studies conducted in the late 1960s and early 1970s confirmed the improvement in migraine with treatment[6]. NICE has published an evidence summary on migraine prophylaxis: flunarizine. Flunarizine is a calcium channel blocker that reduces smooth muscle spasm. Overall, the studies included in this evidence summary suggest that flunarizine is as effective as propranolol or topiramate at reducing the frequency of migraines in adults. In 1 RCT (n=783 adults), flunarizine was as effective as propranolol, each reducing the mean migraine frequency from around 3 at baseline to around 2 per 4 weeks (calculated over the 16-week study duration)[7]. CDSCO has approved Propranolol 40mg (SR Pellets) + Fluarizine 5mg/10mg capsules for the prophylaxis of migraine on 16/03/2010[8].Valproate products are FDA-approved drugs to treat seizures, and manic or mixed episodes associated with bipolar disorder (manic-depressive disorder), and to prevent migraine headaches. In adult Valproate is recommended as 400-600 mg /day for migraine prophylaxis[9]. Very few head to head studies are present using these two drugs as migraine prophylaxis. We have found no study regarding EQ-5D-5L scoring improvement with drug for migraine prophylaxis, which scoring has described five separate parameters for measuring patient's health status. The objective of the study was to assess comparative efficacy of Propranolol plus Flunarizine combination and Sodium valproate (500mg) in reducing migraine headache as measured by comparing change of Frequency (attack per month), MIDAS score, duration of headache and to assess comparative efficacy of two aforesaid treatment groups in improving physical quality of life and the impact on general health related quality of life as elicited by comparing change of EQ-5D-5L Questionnaire and EQ-VAS score.

Materials and method

It was an Interventional study designed as Prospective, randomized, parallel group, open-label, two arm trial. The study done at, Room no 1 in the outpatient department in Department of Neurology, Bankura Sammilani Medical College at Lokepur, Bankura.

Inclusion criteria:

- Adult and adolescent (age > 12 years) patients diagnosed with migraine according to the 3rd edition (beta version) of International Classification of Headache Disorders (ICHDIII) criteria of International Headache Society (IHS),
- Patients, with presence of an indication for prophylactic treatment (intolerable headache attacks that were either debilitating or resulted in significant loss of daily function
- Frequent attacks (≥ 4 attacks per month)

Exclusion criteria

- Other causes of headache
- Major illness
- Any co morbidity
- Pregnant and lactating mother
- Any known allergies to the study drugs

We have done the study for 18 months, from February 2017 to July 2018.

Sample size were calculated by the formula $(z\alpha + z\beta)^2 \times (\sigma_1 + \sigma_2) / (\mu 1 - \mu 2)^2$ as minimum 72 including 20% dropout, where Zα is α error = 1.96, Zβ is β error = 0.84, σ_1- standard deviation of first group,σ_2- standard deviation of second group, both are same as taken from same population and(μ1-μ2) is deviation of MIDAS score from baseline expected after treatment = 5. We have studied reduction in the frequency, which is no. of headache per month, reduction in the duration of headache and MIDAS score. The quality of life was assessed using to EQ-5D-5L questionnaire. It contains 5 headings and each heading contains 5 questions, each was coded in Excel sheet against 1-5 score. A greater score indicates poor quality of life. Each heading analyzed separately. Another scoring done by the EQ VAS that is a visual analogue scale suggested how bad is the patient's health for that day. It is a subjective criterion. Score ranges from 0-100. 0 means worst and 100 means the best one can imagine.We have done the study for 18 months, from February 2017 to July 2018, included all patients who met our inclusion and exclusion criteria. This study was done following the principles of the Declaration of Helsinki for study on human subjects. This study was conducted only after obtaining proper written approval from the Institutional Ethics Committee. Written informed consents were taken from every study patient or their legal representatives. It was registered in Clinical Trial Registry India (CTRI) under Indian Council for Medical Research (ICMR), Government of India. The registration number is **CTRI/2017/07/009074**.After arrival of the patients at neurology OPD, consultant neurologist examined them. Those diagnosed by him, other cause of headache were excluded by history, clinical or relevant imaging (CT scan) and the patients were passed through a printed preformed validated MIDAS questionnaire. Those who scored ≥ 5, were taken as having migraine need prophylactic treatment. At baseline level, a MIDAS score assessment was done. Also a baseline assessment of EQ-5D-5L score &

EQ-VAS score was done. He was also asked to maintain a migraine diary to note the date of attack of headache during every month, and last month total days were collectively noted as frequency. These were accompanied by necessary baseline laboratory investigations, i.e. Complete Blood Count, Blood sugar, Liver function test, Urea, Creatinine, Sodium, Potassium estimation, 12 lead ECG etc. Now this patients were randomly allocated into 2 groups using pre-set computer generated random numbers and were prescribed the following drugs by consultant neurologist.

Group V = Valproate 500 mg Once daily dose

Group PF = Propranolol 40 mg plus Flunarizine 10mg Once daily dose

No adjuvant medicine were given as comorbidities were excluded to avoid possible drug interaction but for controlling the attack in some case abortive concurrent medication were prescribed as and when necessary.

Patients were followed up for two visits, after 12 weeks and 24 weeks interval from the day of starting treatment. On each visit, assessment was done by Duration, Frequency, MIDAS score, EQ-5D-5L score and EQ-VAS score. At the end of follow up after 12 weeks and 24 weeks, all baseline investigations were repeated. The drop outs or withdrawal if any along with reasons for the same were recorded. Data was collected in a specially designed case record form (CRF) by conducting a personal interview with each patient during the clinic visit. Data were entered in Microsoft Excel & checked for accuracy. Data were analyzed with the help of SPSS version 22 and Graph Pad Prizm version 5. Normalcy was checked by the Kolmogorov-Smirnov test and Shapiro-Wilk test. For estimating change in Frequency, MIDAS, EQ-5D-5L & EQ-VAS score within a particular group from baseline, we used Friedman's ANOVA, Repeated measure ANOVA followed by Dunn's &Wilcoxon match pair sign rank test post-hock analysis. Whereas for estimating difference between different treatment groups at different follow up visit we used Mann whitney U and Unpaired t test followed by Dunn's &Tukey's post-hock analysis. All analyses were two sided. P value less than 0.05 was taken as significant.

Result

During entire study period, we encountered a total of 102 patients, of which 27 patients did not meet the inclusion & exclusion criteria. Hence, 75patients were enrolled. But 5 patients were lost to follow up. Final analysis was done on 70 patients.Females were majority (60%) outnumbering the males to a great extent. Maximum numbers of patients (70.38%) belonged to age group of 20-40 years (Table 1). The age distribution data was parametric according to Kolmogorov-Smirnov test. Then we performed Unpaired t test to find out any significant difference in age distribution between the groups. The P value was found to be 0.38. No post hoc test was required.We used three principal variables- to see decrease in Headache Frequency (that is headache days per month), MIDAS Score and EQ-5D-5L score to see in improvement of quality of life. EQ-5D-5L has subgroup of Mobility, Self-care, Usual activity, Pain/ Discomfort and Anxiety/Depression which have level coded from 1-5. 1 signifies best and 5 signifies worst outcome.We performed Unpaired t test for headache frequency to find out any significant difference between groups at baseline as the data parametric. In group V and in group PF Mean± SD was 9.054±2.107 & 8.485±2.152 and p value was 0.078.We performed Mann whitney U to find out any significant difference between groups for MIDAS score and at baseline as the data was non-parametric. Mean± SD was 19.14±3.17 & 19.70±3.09 respectively. P value was 0.0678.We have analysed EQ-5D-5L parameter separately and in group Valproate and in group Propranolol plus Fluarizine combination and the result we found Mean±SD was in case of Mobility 3.378±0.892 &3.0±1.031 with p value 0.2441, in case of Self-care 3.56±0.8 & 3.212±0.96 with p value 0.1538, in case of Usual activity 3.216±1.004& 3.364±1.025 with p value 0.1781, in case of Pain/ Discomfort 3.378±0.728 & 3.545±0.904 with p value 0.5643 and in case of Anxiety/Depression it was 3.622±0.681 & 3.485±0.972 with p value 0.0505. So no significant difference was found at baseline.We have also studied EQ-VAS (Visual Analogue Scale) Score for intensity and duration of headache also. In EQ-VAS 0-100 marking is present, where 0 means the worst and 100 means the best health one can imagine. Duration of headache was expressed in hours. Mean ±SD was 35.023±8.476 and 37.27±12.44 in Group V and PF respectively and p value was 0.0951 at the baseline, when we studied EQ –VAS and Mean± SD in case of duration of headache was 11.76±3.427 and 10.27±2.44 and p value was 0.1105. So, in both occasion we found non-significant result.Change of Headache Frequency done within group V (Repeated Measure ANOVA) followed by Wilcoxon match pair post-hoc test, and Mean± SD was 9.054±2.107, 6.027±1.236 and 2.649±1.317 respectively from baseline to follow up and p value was very much significant <0.0001. It was significant in both the

follow up. Same observation with group PF Mean± SD was, 8.485±2.152, 5.394±1.345 and 2.152±1.121 respectively from baseline to follow up and p value was very much significant <0.0001 (Table 2 &Figure 2). It was significant in both the follow up. We performed Unpaired t test to find out any difference in mean Headache Frequency between the groups over three follow ups and found the result in first follow-up p value was 0.071 and in second follow-up p value was 0.152. So, both the drugs were equally effective in headache frequency reduction.Change of MIDAS Score done within group V (Friedman ANOVA) followed by Dunn's post-hoc test, and Mean± SD was 19.14± 3.172, 10.34±2.599 and 5.94±1.966 respectively from baseline to follow up and p value was very much significant <0.0001. It was significant in both the follow up. Same observation with group PF Mean± SD was 19.7±3.097, 10.94± 2.772 and 5.634±2.329 respectively from baseline to follow up and p value was very much significant <0.0001 (Table 3 & Figure 3). It was significant in both the follow up. We performed Mann-whitney U test to find out any difference in mean Headache Frequency between the groups over three follow ups and found the result in first follow-up p value was 0.68and in second follow-up p value was0.89. So, both the drugs were equally effective in MIDAS Score reduction.After doing an exhaustive statistical test on the 5 parameter of EQ-5D-5L data, we came to the conclusion that both the drugs are very much effective and significant change (0.05) noted in Valproate and Propranolol plus Fluarizine combination group from baseline to first follow up and baseline to second follow up except in case of mobility where group PF shows no improvement on both the occasion. In between group analysis by unpaired t-test significant changes is showing in case of Anxiety/Depression where group V is more effective (p values 0.04 and 0.01 in 1st and 2nd follow up respectively) (Table 4).

Change of EQ-VAS done within group V (Repeated Measure ANOVA) followed by Wilcoxon match pair post-hoc test, and Mean was 35.03, 51.94 and 68.48 respectively from baseline to follow up and p value was very much significant. Same observation with group PF. Mean was 37.27, 51.33 and 65.03 respectively from baseline to follow up and p value was very much significant (Figure 4). It was significant in both the follow up. No significant change in between groups was observed as tested by unpaired t test.

Change of headache duration within group V (Friedman ANOVA) followed by Dunn's post-hoc test, and Mean was 11.76, 6.703 and 3.514 respectively from baseline to follow up and p value was very much significant. Same observation with group PF. Mean was 10.27, 6.545 and 3.424 respectively from baseline to follow up and p value was very much significant (Figure 5). It was significant in both the follow up. No significant changes in between groups were observed as tested by Mann whiteney U test.

Fig1:Demographic characteristic

Table 1 : Age distribution-group wise

Group	Mean (Yrs)	SD (Yrs)
V	31.35	9.025
PF	30.61	9.702

Table 2:Reduction of headache frequency group wise

	V	PF
Baseline	9.054	8.485
1st Visit	6.027	5.394
2nd Visit	2.649	2.152

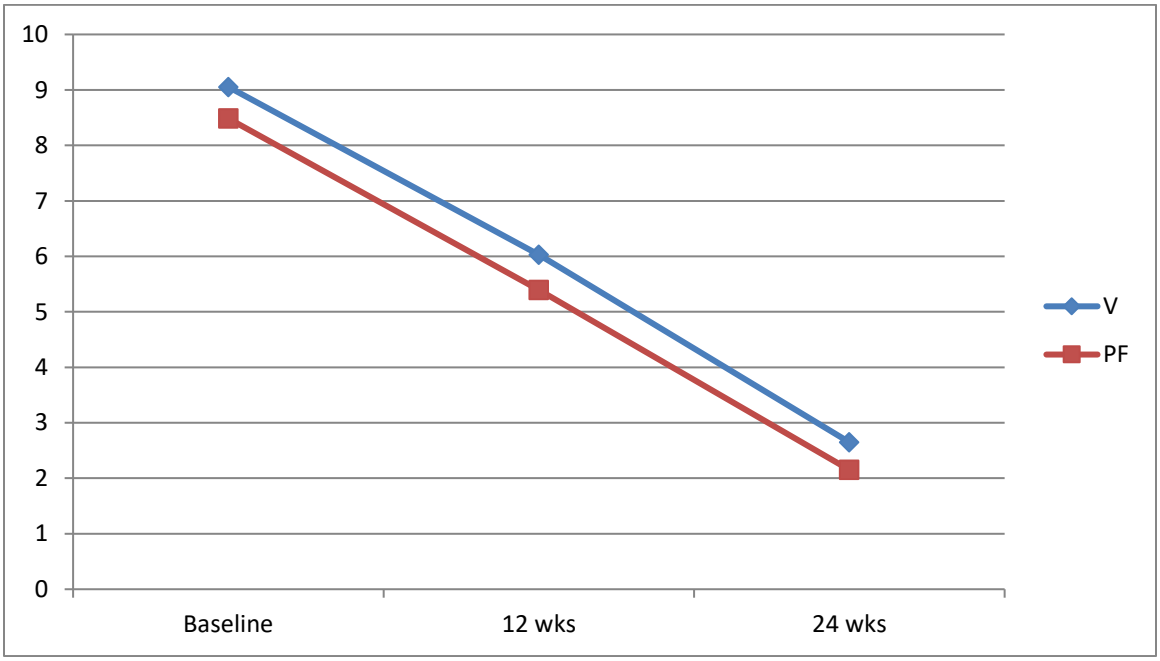

Fig 2: Reduction of headache frequency group wise

Table 3: Reduction in MIDAS Score group wise

	V	T
Baseline	19.14	19.7
1st Visit	10.54	10.94
2nd Visit	5.541	5.364

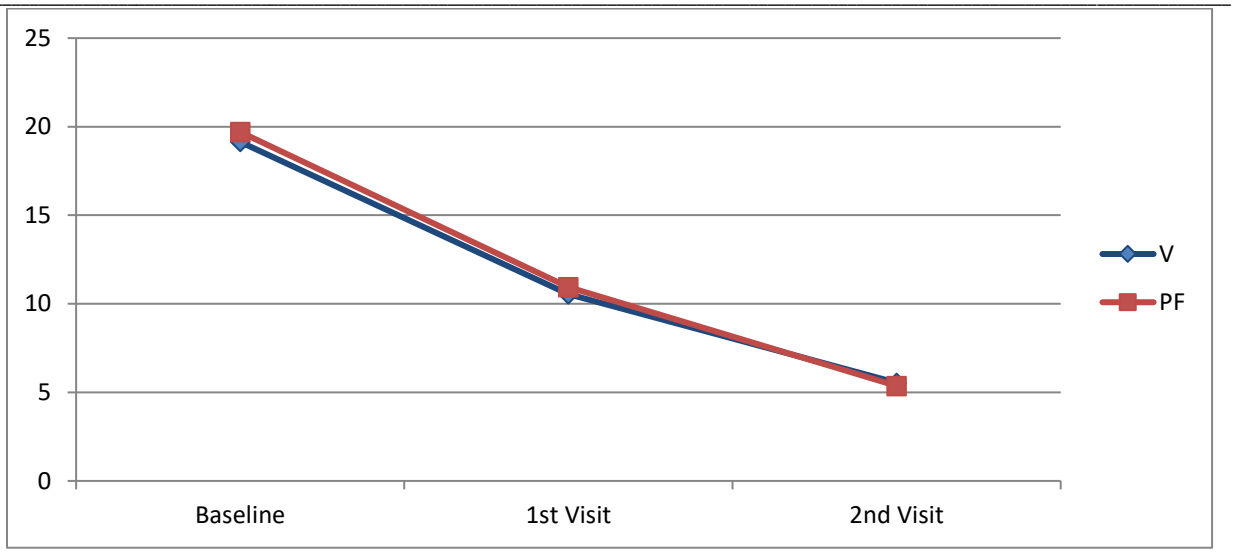

Fig 3: Reduction of headache MIDAS Score group wise

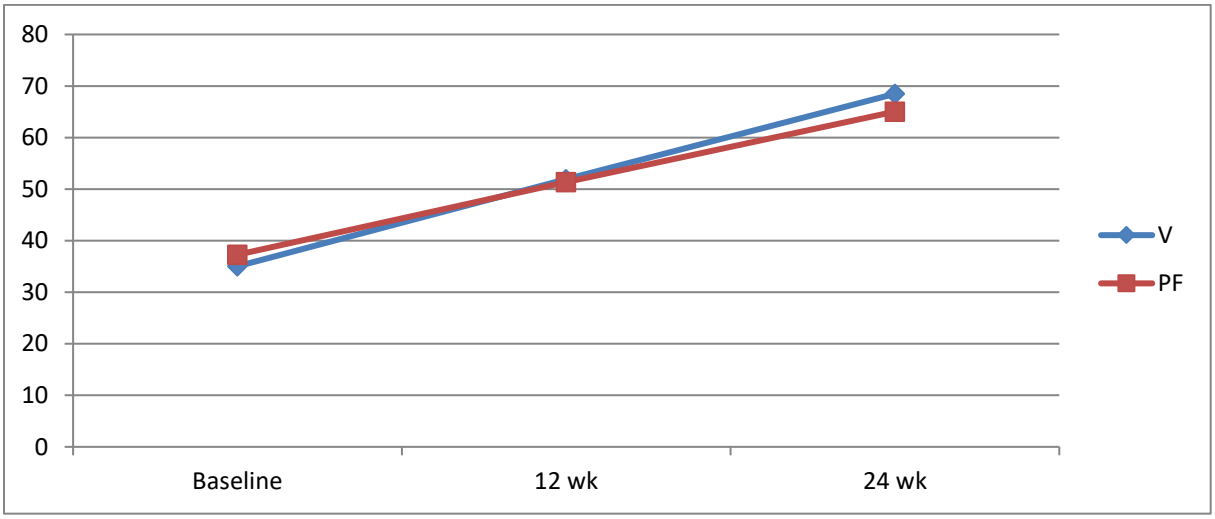

Fig 4:Changes in EQ-VAS Score

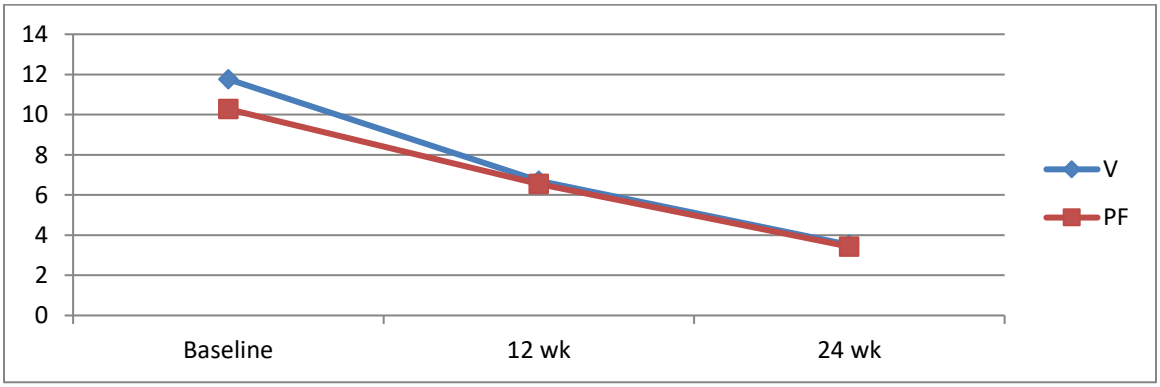

Fig 5 :Reduction in headache duration

Table 4 :Change of quality of life

	Post hoc test	Group shows change
Mobility / Self- care / Usual activity / Pain &Discomfort / Anxiety & Depression	Within group	ALL group Only PF shows no change in Mobility
	Between group	Group V vs PF in Mobility & Anxiety & Depression

Discussion

Though several treatment options are there, the management of migraine is still a challenge to physicians. Long term compliance and ADR is the main hindrance to treat migraine. Beside this, the poor quality of life added the poor outcome. Very often patients use to live with the headache and productivity in the social life and in work place is lost. It is thus of utmost important to find out the treatment with a drug (s) with optimum balance between efficacy and safety. We have made extensive search through published literature, but failed to find any study which includes these drugs with all this parameter for head to head comparison for treatment of migraine in OPD setting.We have clearly seen female preponderance with maximum patients involving 2nd to 4th decade of life which was similar to other migraine related studies. In the study, Evaluation of propranolol, flunarizine and divalproex sodium in prophylaxis of migraine by Majid F. Bhat et al in case of frequency of migraine attacks per month, difference was reached as early as the 1st month for the all the three groups and remained statistically significant throughout the treatment phase. There was a progressive and statistically significant (P<0.001) decrease in the average duration of the migraine attacks in all the three treatment groups. Significant reduction in MIDAS scores was noted at the end of treatment period when compared to the baseline in the treatment group[10]. We found no difference in our study. Fifty-five patients completed the study by Ganesh N dhakale et al at Nagpur, Maharastra. At the end of the treatment, both sodium valproate and propranolol caused a significant (P < 0.0001) reduction in frequency, severity, and duration of migraine headache. Propranolol caused significantly greater reduction in the severity of headache (P = 0.0410) than sodium valproate. The percentage of responders was 60% in sodium valproate group and 70% in propranolol group[11]. We found insignificant result between the group probably because geographical location. In other studies we have seen that both flunarizine and propranolol have demonstrable efficacy in the prophylaxis of migraine,[12]but no significant difference in efficacy was observed between sodium valproate at 1000 mg versus flunarizine at 10 mg daily maintained for 4 weeks[13]. Meta-analysis with 10 small trials done by Adam R. Aluisio et al and in two studies (one comparing divalproex sodium vs. propranolol and another evaluating sodium valproate vs. flunarizine) no significant differences in the proportion of responders were identified[14]. Chowdhury MI et al have done a study at Headache clinic at Dept. of Neurology of BSMMU from Nov'05 to Dec'06. It is shown that reduction in headache frequency (no of attack/3month) was significant in Propranolol group in Valproate group, no significant difference between the groups. Reduction in headache days /3month had also same outcome. Reduction in MIDAS score was 47.73 from 16.08 with p value <0.001 in Propranolol group and 49.62 to 17.41 with p value <0.001with Valproate group, no significant difference between group[15]. Similar result was obtained from our study but with combination of Propranolol plus Flunarizine. The reasons behind combining the drugs were dose reduction as well as reduction of ADR. We have searched literature also that combining the drugs had similar outcome. Bordini CA et al,1997 have done a double-blind trial on Propranolol vs flunarizine vsflunarizine plus propranolol in migraine without aura prophylaxis on fourty-five migraine without aura patients and they underwent a parallel double-blind trial aiming the comparison of the effects of propranolol 60 mg/day to flunarizine 10 mg/day and to propranolol 60 mg/day plus flunarizine 10 mg/day simultaneously. It was not found statistical differences between groups[16]. We have failed to found any study regarding EQ-5D-5L scoring.

Conclusion

In this open-label, parallel group, 24 weeks (first follow up12 wk and second follow up 24 wk), interventional study we found that Valproate and Propranolol plus Flunarizine combination both were

highly effective in migraine prophylaxis. There were no differences between the groups within first and second follow-up. Migraine frequency and duration was reduced, as well as the migraine associated disability assessed by MIDAS score. Quality of life was also improved significantly in those groups from baseline which may be due to both pain reduction and also improve in usual activity, mobility and anxiety/depression with those two groups of drugs, but Valproate was proved with better outcome than the other group.

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