RESEARCH PAPER | Medical Science | Volume : 5 | Issue : 8 | August 2015 | ISSN - 2249-555X

Combination Prophylactic Pharmacotherapy In Refractory Migraine – A Study

KEYWORDS: Refractory migraine, monotherapy, combination prophylactic drug therapy

Dr.Ch.Ramakrishna Rao

Dr.Ch.Ramakrishna Rao, MD DMAssociate Professor of Neurology, Siddhartha Medical College,Vijayawada,

Dr.W.Maruthi

Dr.W.Maruthi, MD Associate Professor of Physiology, Guntur Medical College, Guntur,

ABSTRACT *Introduction. Migraine is the most frequent neurologic disease observed in the clinical practice. This primary headache is associated with an important socioeconomic impact and the World Health Organization recognized the disorder as a major public health problem, by ranking it at 7th place among all worldwide diseases causing ictal disability.Migraine is a paroxysmal disorder with a natural fluctuation between a low and a high frequency pattern in part influenced by modifiable and non-modifiable risk factors. Increased attack frequency can lead to the so-called 'refractory migraine', which then becomes less responsive to acute as well as prophylactic migraine medications. Despite substantial advances in migraine therapy, some individuals with migraine are refractory to guideline-based treatment. However until a well-accepted definition is formulated, evidence-based treatment recommendations for refractory migraine cannot be generated.MaterialsandMethods. In this study, initially, an attempt is made to identify patient populations attending the outpatient department of Neurology, Government General Hospital, Vijayawada between the period of March, 2008 and May, 2015, those may be appropriate to consider for combination preventative therapy. Four classes of drugs are available in the outpatient department and these are β-blockers, (propranolol), calcium channel blockers (flunarazine), antidepressants (amitryptiline) and antiepileptics (sodium valproate). A total of 3,465 subjects were treated for migraine during the period. Out of these, 2874 were women and 591 were men constituting 83% women and 17% men respectively.Results. The results indicate that about 43% of women subjects and about 56% of men subjects are benefited from combination preventive drug therapy for refractory migraine.Discussion. Migraine is a paroxysmal disorder with a natural fluctuation between a low and a high frequency pattern.Till date, there is ample data to suggest that effective acute treatment of migraine is associated with improved responses and decreased disability. But, the potential disease-modifying effects of migraine preventives have not been studied extensively. The success of a physician, or to say, the neurophysician lies in meeting the demands of this subpopulation of the refractory migraineurs. Data guiding duration of preventive therapy are limited. Based on the studies it is suggested that preventative therapy be continued for at least one year.Conclusions. Although it is unknown if migraine preventative therapy confers disease modification, preventive therapy is frequently associated with pain relief and reduction in disability. Limited data and clinical experience suggest that combination therapy should be considered in migraineurs who present with disability and a history of repetitive failed preventive regimens (monotherapies) in the past.*

Introduction

Migraine is the most frequent neurologic disease observed in the clinical practice. This primary headache is associated with an important socioeconomic impact and the World Health Organization recognized the disorder as a major public health problem, by ranking it at 7th place among all worldwide diseases causing ictal disability. Migraine, a syndrome that affects 10 to 12% of the general population, is defined on the basis of the clinical features of a typical attack[1]. Migraine syndrome is a moderate to severe, recurrent, unilateral, throbbing headache, lasting for hours to days, which is generally accompanied by nausea, photophobia, and phonophobia, and worsened by routine physical exertion[2]. The purpose of migraine-preventive therapy is to reduce attack frequency, severity, and impact and to act synergistically with abortive therapy to improve its effectiveness. The ultimate goals of preventive therapy are – enhance health-related quality of life (HRQoL), improve the sufferer's level of functioning, and prevent disease progression. These goals are achieved using certain guiding principles[3] – establishing the correct diagnosis and diagnostic category, assessing the overall impact of the condition, including medical, social, and psychological aspects, selecting and optimizing drug dosing, allowing the drug for an adequate trial period (typically 2 to 3 months), thorough discussion of the treatment plan with patients including adverse effects of drugs, goals and expectations of the therapy, and compliance. Candidacy for migraine prevention depends on several factors including – attack frequency, degree of disability, response to acute treatment(s), lifestyle, patient's wishes, and migraine subtype. The choice of appropriate preventive therapy should be individualized by taking the following into consideration[3] – available evidence of drug efficacy, balance between therapeutic effects and side effect potential of the drug, compliance factors, and comorbid conditions. Migraine-preventive therapies include pharmacological and nonpharmacological approaches, such as bio-feedback. The more conventional preventive strategy involves the long-term use of a preventive drug. While the prognosis for the majority of patients is good, approximately 5-14% of episodic migraineurs will progress to refractory chronic headache. And unfortunately, it has been estimated that only 14% of refractory headache sufferers will remit to less than one headache per week over one year[4]. Thus, while migraine itself confers substantial personal and societal burden, refractory chronic migraine may extract an even greater toll[5,6,7]. Refractory migraine patients are those for whom adequate trials of preventive therapies at adequate doses have failed to reduce headache frequency and improve headache-related disability. Migraine is a paroxysmal disorder with a natural fluctuation between a low and a high frequency pattern in part influenced by modifiable and non-modifiable risk factors. Increased attack frequency can lead to the so-called 'refractory migraine', which then becomes less responsive to acute as well as prophylactic migraine medications. The response to a preventive drug varies from person to person and fluctuates over time.

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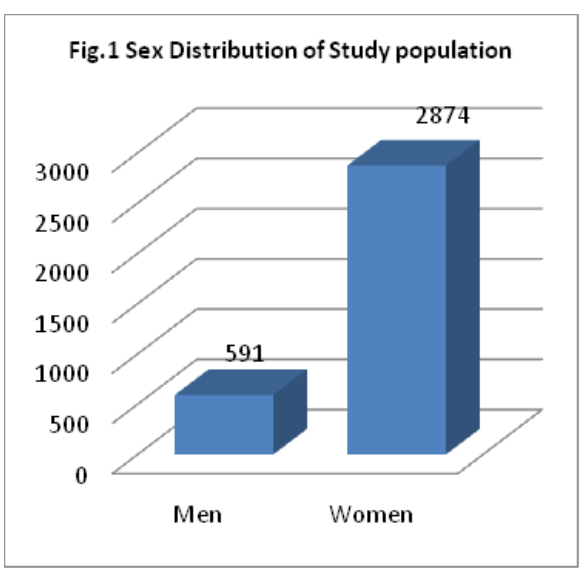
Moreover, comorbidities like depression, insomnia, anxiety, hypertension and obesity act as worsening factors in the chronification process. Despite substantial advances in migraine therapy, some individuals with migraine are refractory to guideline-based treatment. Additionally recent studies revealed that the majority of migraine patients are undertreated in terms of use of prophylactic drugs, thus favouring the progression of migraine into chronicity. Intractable migraine is another term that has been used interchangeably for the headache types we are addressing. If we go through the semantic of these terms, it is easy to realize that they describe two different conditions. While a refractory migraine can improve or worsen over time also in relation to events independent of the headache, an intractable migraine carries in itself the implication that the condition may never be improved. The term "refractory", which is more frequently used in the literature, should be preferred because it better emphasizes the lack of treatment response. However until a well-accepted definition is formulated, evidence-based treatment recommendations for refractory migraine cannot be generated.

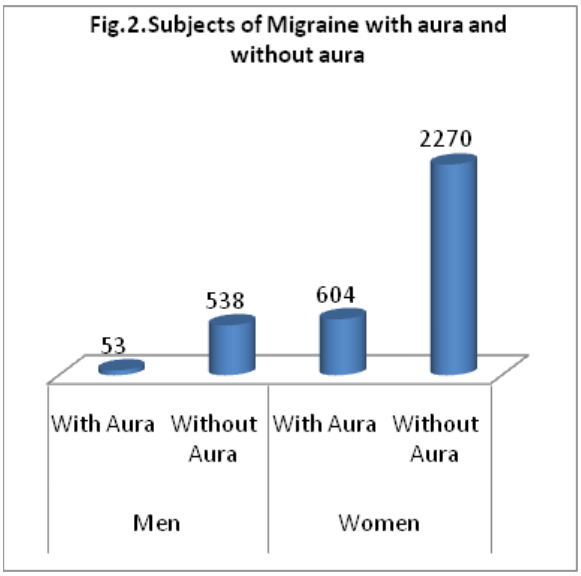
Materials and Methods

The proposed Refractory Headache Special Interest Section (RHSIS) Refractory Migraine criteria include failure of at least 2 *preventive* medications from 2 different classes; these patients warrant consideration of preventive polytherapy. Usually, a trial of 3-months' period is given for a drug under monotherapy to prove its efficacy.

In this study, initially, an attempt is made to identify patient populations attending the outpatient department of Neurology, Government General Hospital, Vijayawada between the period of March, 2008 and May, 2015, those may be appropriate to consider for combination preventative therapy. Four classes of drugs are available in the outpatient department and these are β-blockers, (propranolol), calcium channel blockers (flunarazine), antidepressants (amitryptiline) and antiepileptics (sodium valproate). A total of 3,465 subjects were treated for migraine during the period. Out of these, 2874 were women and 591 were men constituting 83% women and 17% men respectively (**Fig 1**).



Out of the 2874 women, 604 women were diagnosed to be suffering from migraine with aura, constituting 21% and out of 591 men, 53 men were diagnosed to be suffering from migraine with aura, constituting 9% (**Fig 2**).



All the patients were initially started with monotherapy, basing on the patient selection, with the drugs available in the department. After a 3 months' trial period with first drug, it was found that out of 2874 women, 862 women and out of 591 men, 66 men did not get satisfactory relief from headache. Later, a second drug was started discontinuing the first one and again, a 3 months' trial period was given for the second drug. 265 out of 862 women and 25 out of 66 men got satisfactory relief from the headaches. The remaining 597 women and 41 men, who still failed to respond to the second drug, were then treated with combination therapy adding the third drug to the second drug. The details of the treatment plan was shown in the Table.1 below.

Table .1 Treatment plan used in the study

First drug used	Second drug used	Combination used
Amitryptiline	Sodium valproate	Sodium valproate +Propranolol
Sodium valproate	Amitryptiline	Amitryptiline +Flunarazine
Propranolol	Flunarazine	Flunarazine +Amitryptiline
Flunarazine	Propranolol	Propranolol + Amitryptiline

Results

Of the 597 women, who received combination preventive drug therapy, 255 women subjects got substantial relief from their headache episodes in terms of frequency and severity within one month period. Of the 41 men subjects, who received combination preventive drug therapy, 23 men got substantial relief from their headache episodes in terms of frequency and severity in about 4 to 6 weeks period. The results indicate that about 43% of women subjects and about 56% of men subjects are benefited from combination preventive drug therapy for refractory migraine.

Discussion

Migraine is a paroxysmal disorder with a natural fluctuation between a low and a high frequency pattern.Till date, there is ample data to suggest that effective acute treat-

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ment of migraine is associated with improved responses and decreased disability. But, the potential disease-modifying effects of migraine preventives have not been studied extensively[8,9]. It is plausible that migraine preventives may possess such effects, as several neurological disorders (channelopathies) with pathophysiological similarities to migraine (including multiple sclerosis and epilepsy) have data suggesting preventative therapy limits disease burden, ie, results in "disease modification"[10,11,12]. Ultimately, our goal should be to prevent the development of refractory migraine. However, refractory migraine is defined by a poor response to both pharmacologic and nonpharmacologic treatment. Thus, in refractory migraine sufferers, it is natural to consider combination preventive treatment for this group of patients. And herein, we have focussed on the treatment of developed refractory disease.

As research in migraine polytherapy is in its infancy, most of the suggestions are based on the evidence of randomized controlled trials of medications showing efficacy for migraine prevention as monotherapy. Concurrent risk factors and/or comorbidities frequently guide preventive choices and may warrant consideration of combination therapy. Several psychiatric disorders (including depression and anxiety) and medical disorders (including stroke, epilepsy, and cardiovascular disease) are comorbid with migraine[13,14]. Additionally, other factors associated with migraine chronification include age, gender, obesity and medication overuse. While some of these risk factors, including age and gender, are not modifiable, others such as obesity and medication overuse are modifiable[15,16]. Although monotherapy may be preferred for preventive therapy, this may not always be attainable clinically.

Migraine preventives are predominantly from one of 3 drug classes: antiepileptic, antidepressant, and antihypertensive agents[17,18,19]. Choice of preventives may be based on the presence or absence of comorbidities or risk factors. Migraine-specific combination therapy is largely anecdotal and based on clinical experience. And though unproven, factors including a strong family history and an earlier age of onset may warrant consideration for migraine-specific combination therapy. Largely, consideration of combination therapy based on disability and history of repetitive failure of previous preventives.

The mechanism of action of β-blockers in migraine is not entirely known. Propranolol has membrane stabilizing activity, possesses affinity for 5-HT sites in the brain, and also inhibits cytokines. In the present study, in patients, who inadequately responded to antiepileptics or antidepressants, the addition of β-blocker is considered. There is evidence that the combination of a β-blocker and an antiepileptic (either valproic acid or topiramate) is effective in refractory migraine, even in the absence of response to the β-blocker alone[20,21]. Additionally, in hypertensive migraineurs, or those with anxiety or aggressive behavior, the addition of propranolol is preferred.

Calcium channel antagonists, flunarazine, block the transmembrane influx of Ca^{2+} across cell membranes through slow, voltage-dependent channels[22]. Several properties of these agents may mediate their effectiveness in migraine prophylaxis. Flunarazine exerts minimal effect on cerebral vessels in therapeutic doses, yet protects against excessive Ca^{2+} influx and release during cerebral ischemia. Flunarazine also inhibits synthesis and release of nitric oxide, a substance implicated in migraine pain. However, as the brain contains a high density of calcium channel binding sites – and evidence suggests that calcium channel antagonists affect neurotransmission – interaction with central nervous system (CNS) transmission may be the primary mechanism for their effectiveness in migraine. Calcium channel antagonists may be considered for polytherapy in migraineurs without contraindications to their use. They could be used in combination with antiepileptics (such as topiramate) or antidepressants (such as amitriptyline). Calcium channel antagonists may have a significant role in patients with hemiplegic migraine, a disorder associated with calcium channel mutations[23].

Tricyclic antidepressants (TCAs) and dual serotonin norepinephrine reuptake inhibitors (SNRIs) have shown efficacy in migraine, although selective serotonin reuptake inhibitors (SSRIs) may be effective for headaches associated with premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD)[24,25,26]. As with antihypertensives, multiple actions are responsible for the utility of antidepressants in migraine prophylaxis. The analgesic effect seems unrelated to their antidepressant action and is not attributed to inhibition of serotonin reuptake. TCAs also block alpha-adrenergic, histaminic, and muscarinic receptors. It is likely that their benefit involves effects on central pain pathways (via inhibition of serotonin and norepinephrine reuptake and attenuation of central sensitization via N-methyl-D-aspartate (NMDA) receptor agonism). Peripheral analgesic actions may also play a role. Noradrenergic agonist activity in the locus ceruleus is associated with gating attention to stimuli, including nociceptive stimuli; this may explain the relatively better performance in pain management of antidepressants that augment norepinephrine. Antidepressants, particularly the SSRIs, should be used with caution in bipolar disorder as they may unmask mania.

As depression, anxiety, and panic disorder are comorbid with migraine, antidepressants are a logical choice in their presence. In particular, a TCA such as amitriptyline or nortriptyline can be helpful in refractory migraine when weight loss is *not* desirable. These agents may be used in conjunction with an antiepileptic such as valproic acid. Alternatively, in an obese depressed patient, protriptyline in conjunction with topirimate may be useful. In this setting, antihypertensives such as verapamil and propranolol may be undesirable due to their potential for prolongation of the PR interval and QTc interval, respectively, as well as their potential for weight gain and decreased exercise tolerance. It is to be noted, however, that TCA doses required for management of depression are greater than those needed for migraine prevention and may not be as well tolerated. TCAs may also be considered in migraineurs who suffer from fibromyalgia; in this setting, the combination of a TCA and gabapentin or pregabalin could benefit both disorders. Although SSRIs are not effective for migraine prevention, they are indicated for PMS/PMDD. In migraineurs with these disorders, SSRIs are effective. If migraines are also present throughout the cycle, the combination of an SSRI with an antiepileptic or antihypertensive may be beneficial.

Topiramate and valproic acid are the only FDA-approved antiepileptics for migraine, although others have shown efficacy[27]. Several relevant mechanisms of actions for antiepileptics in migraine prophylaxis have been demonstrated. Both topiramate and valproic acid block sodium channels. However, both topiramate and valproic acid also modulate gamma-amino butyric acid (GABA)[27]. Antiepileptics can be successfully combined with antidepressants to treat refractory migraine. Topiramate can be used in combination with

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a TCA or SNRI, antihypertensive or another antiepileptic. When obesity or diabetes complicates refractory migraine with depression, topiramate is chosen for polypharmacy with an antidepressant. Antiepileptics can also be utilized in refractory epilepsy with mood or personality disorders. Topiramate may not only be helpful for prevention of migraine in patients with bipolar or borderline personality disorder, but serve as adjunctive therapy of these psychiatric conditions.

Guidelines do not currently exist for combination therapy in migraine. Nevertheless, logic suggests that certain combinations may be useful, particularly in refractory migraine depending upon the mechanism of action of the preventive drugs. The present study has amply revealed the fact that combination preventive drug therapy is associated with marked improvement in symptom relief. The subpopulation of refractory migraineurs pose a problem in the regular clinical practice. The refractory migraineurs are prevented from attending to their ADL because of the severity and frequency of the headache episodes. The success of a physician, or to say, the neurophysician lies in meeting the demands of this subpopulation of the refractory migraineurs. Data guiding duration of preventive therapy are limited. Available data indicates the duration of combination therapy to stretch for period of about one year. Wober et al and Pascual et al suggest that the current practice recommendation of 3-6 months of preventive treatment may be inadequate for many patients. Based on their studies it is suggested that preventative therapy be continued for at least one year.

Conclusions

Although it is unknown if migraine preventative therapy confers disease modification, preventive therapy is frequently associated with pain relief and reduction in disability. Limited data and clinical experience suggest that combination therapy should be considered in migraineurs who present with disability and a history of repetitive failed preventive regimens (monotherapies) in the past. Combination therapy may also be beneficial for migraineurs with comorbid disorders, medication-overuse headache, early onset, and strong family history. Based on the extreme paucity of data with regard to combination therapy and refractory migraine, extensive research is needed to guide treatment of this subgroup of migraineurs.

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