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A PROSPECTIVE OBSERVATIONAL STUDY OF DRUG UTILIZATION FOR COMPARATIVE ANALYSIS OF EFFICACY OF SUMATRIPTAN, NAPROXEN AND A FOUR COMPONENT ERGOTAMINE BASED COMBINATION IN MIGRAINE WITHOUT AURA

Pharma

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ABSTRACT

Background: Migraine is primary headache disorder characterized by recurring attacks of pain and associated symptoms. Ergotamine has been considered very effective preparations for aborting acute attacks of migraine without aura but in recent times Triptans have proven to be very promising as well. **Objective:** The aim of our study was to compare the efficacy of Sumatriptan, Naproxen and Ergotamine based four-component drug combination in the treatment of moderate to severe acute attacks of migraine without aura. **Materials and Methods:** Study was designed as prospective, observational, randomized, parallel arm and unicentric conducted in neurology department of a tertiary care hospital of North India. The enrolled patients having migraine without aura were randomised in four treatment groups. Group 1(n=49) received Sumatriptan (100 mg), Group 2(n=46) received a combination of Sumatriptan (85 mg) and naproxen (500 mg), Group 3(n=50) received Naproxen (500 mg) and Group 4(n=44) received a combination of Ergotamine (1 mg) + Caffeine (100 mg) + Paracetamol (250 mg) + Prochlorperazine (2.5 mg). **Results:** In the first part of the study, combination of sumatriptan and naproxen worked significantly better than sumatriptan alone in higher dose in terminating the Migraine attack within 2 hrs. In the second part combination of Sumatriptan (85 mg) and naproxen (500 mg) worked significantly better in ensuring sustained pain relief at 24 hours as compared to Naproxen (500 mg) alone. **Conclusion:** Combination therapy with Sumatriptan and Naproxen remains a promising approach for treating acute migraine and achieving sustained pain-free outcomes, making it a potentially preferable option in clinical practice for migraine management.

KEYWORDS

Efficacy, Fixed dose combination, Headache, Pain

INTRODUCTION

Migraine is usually an episodic headache associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache[1].In the GBD 2015 study, for both males and females under the age of 50, it was ranked as the third leading cause of disability globally. For migraine, global age-standardised prevalence was 14·4% (13·8–15·0) overall: 18·9% (18·1–19·7) for women, and 9·8% (9·4–10·2) for men[2].

A useful description of migraine is a recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures[1].

The pathogenesis of migraine headache is complex, involving both neural and vascular elements[3]. A migraine attack has three phases: premonitory (prodrome), headache phase, and postdrome, each has distinct and sometimes disabling symptoms. About 20–25% of migraine patients have a fourth phase i.e. Aura[1].

The diagnosis of migraine is made on the basis of criteria led by Headache Classification Committee of the International Headache Society (IHS) as per The International Classification of Headache Disorders, 3rd edition (ICHD-3)[4].

For an acute attack of migraine NSAIDS, ergot alkaloids and triptans are considered as mainstay of treatment of which NSAIDS are mostly prescribed. Many combinations of above-mentioned drugs are also been frequently prescribed these days. Patients in case of migraine are usually on polypharmacy for a longer duration of time so are more susceptible to development of ADRs.

NSAIDS play an important role in early migraine attack. The combination of acetaminophen (paracetamol), aspirin, and caffeine has been approved for use by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate treatment of migraine. NSAIDs (including aspirin), nonopioid analgesics, acetaminophen, or caffeinated analgesic combinations (e.g. aspirin + acetaminophen + caffeine) are used for mild.to.moderate attacks and migraine specific agents (triptans, dihydroergotamine [DHE]) for moderate or severe attacks and mild.to.moderate attacks that respond poorly to NSAIDs or caffeinated combinations[5].

Drug utilization research was defined by WHO in 1977 as “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences. The ultimate goal of drug utilization research must be to assess whether drug therapy is rational or not[6].

This present study deals with drug utilization study for acute treatment of migraine and assessment of their comparative efficacy.

The triptans are Indole derivatives. The vasoconstrictive properties of triptans are mediated by an action on 5-HT1B in arterial smooth muscle. On the other hand, although sumatriptan-mediated vasoconstriction they can dose-dependently increase blood flow velocity in middle cerebral vessels, because these vascular changes are not temporally related to the resolution of the migraine attack[7]. The triptans are also thought to inhibit the abnormal activation of peripheral nociceptors. In an experimental model of migraine, called sterile neurogenic inflammation, an abnormal activation of nociceptors in the dura mater triggers vascular changes, including plasma protein extravasation (PPE)[8,9].

Naproxen is Propionic acid derivative and a methoxynaphthalene. It is an established non-selective NSAID and is useful as an analgesic, anti-inflammatory and antipyretic. Similar to other NSAIDs, the pharmacological activity of naproxen can be attributed to the inhibition of cyclo-oxygenase, which in turn reduces prostaglandin synthesis in various tissues and fluids including the synovial fluid, gastric mucosa, and the blood[10].

Ergot is the product of a fungus (Claviceps purpurea) that grows on rye and other grains. The pharmacological effects of the ergot alkaloids are varied and complex; in general, the effects result from their actions as partial agonists or antagonists at serotonergic, dopaminergic, and adrenergic receptors. The spectrum of effects depends on the agent, dosage, species, tissue, physiological and endocrinological state, and experimental conditions[10].

Caffeine may work synergistically with ergotamine by constricting

cerebral vasculature or enhancing its GI absorption. The vasoconstrictive effects of caffeine are due to its antagonistic properties at adenosine A1, A2A, and A2B receptors. Implications point to adenosine receptors in vasodilation. The mechanism of caffeine's rate-accelerating effect appears to be due to its ability to increase ergotamine's water solubility and decrease gastric pH[11].

Acetaminophen is a p-aminophenol derivative with analgesic and antipyretic activities. Although the exact mechanism through which acetaminophen exert its effects has yet to be fully determined, acetaminophen may inhibit the nitric oxide (NO) pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate (NMDA) and substance P, resulting in elevation of the pain threshold[12].

MATERIALAND METHODS

Study Design, Location And Duration

This Study was conducted after prior permission and approval from Institutional Ethics Committee of Moti Lal Nehru Medical College, Prayagraj. It was designed as randomized, prospective, open labelled, parallel group study which was conducted at a single Centre of Swaroop Rani Nehru Hospital (Moti Lal Nehru Medical College, Prayagraj), India, A tertiary Care Centre in North India over a period of 1 calendar year from July 2019 to June 2020.

Inclusion Criteria

Patient of either sexes, with age ≥ 18 years, with confirmed diagnosis of migraine based on clinical presentation and/or criteria proposed by Headache Classification Committee of the International Headache Society (IHS) as per The International Classification of Headache Disorders, 3rd edition (ICHD-3) and who is willing to give consent

Exclusion Criteria

Age < 18 years with any other types of headaches not confirmed to be migraine including Headache attributed to trauma or injury to the head and/or neck, cranial and/or cervical vascular disorder, non-vascular intracranial disorder, Infection, Homeostasis or Headache attributed to a substance or its withdrawal. The exclusion criteria also include Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure, headache associated with psychiatric disorder, painful lesions of cranial Nerves and other facial pain. Those not willing to give consent are also excluded.

METHOD:

On the very first visit, patients were evaluated for general information, present and past symptoms, General and systemic Examination and the symptoms related to Migraine. Patient diagnosed as a case of Migraine attending the outpatient department of Swaroop Rani Hospital, Moti Laal Nehru medical College, a Tertiary health care centre, were enrolled after selecting them on basis of inclusion and exclusion criteria after signing the consent from provided to them in both Hindi and English language or any other language of their preference.

The present study aims at evaluating efficacy of four commonly used drugs and combinations in acute treatment of Migraine namely Sumatriptan (100mg), Naproxen (500 mg), a combination of Sumatriptan (85 mg) and naproxen (500 mg),) and a combination of Ergotamine (1 mg) + Caffeine (100 mg) + Paracetamol (250 mg) + Prochlorperazine (2.5 mg). These drugs or combination were most commonly used in the outpatient department of Swaroop Rani Hospital, Moti Laal Nehru medical College.

The patients were advised to take single dose of drug which was prescribed to them during moderate to severe migraine attack. The patients were told to maintain a Headache dairy in which they were instructed to note presence and absence of headache, functional disability, need for a rescue medication and associated symptoms such as Nausea, vomiting, photophobia, phonophobia at 0 hour (baseline), after 2 hrs and after 24 hrs. Rescue medication was advised only if headache persisted beyond 2 hours or recurred.

Efficacy was evaluated by primary outcome determining the proportion of patients with having no headache pain at after dosing at 2 hrs. The outcome was measured by reduction in mean headache severity at 2 hours post dose compared to baseline headache severity.

The secondary outcome of efficacy evaluation was the proportion of patients who were "sustained pain-free," defined as having no headache pain at 2 hours after dose, with no use of rescue medication and no relapse of headache pain within 24 hours (24-hour sustained pain-free).

Sample Size Calculation:

Sample size (N) = Z 1-α/2 2 x p (1-p) / d2

Here

Z 1-α/2 = is standard normal variate (at 5% type 1 error (P < 0.05) it is 1.96.

p = Prevalence in India based on previous studies is 14.1%[13].

d = Precision or allowable error. This value can be chosen by investigator. I have taken it to be 5% and at type I error of 5 %.

On putting all the values in above formulae, I have calculated total sample size

(N) = 185

On putting all the values in above formulae, calculated total sample size was 185 and with consideration of 10% loss of sample during the study, total sample size was calculated to be= 204

After the Selection of Patients based on inclusion and exclusion criteria, they were randomised by random number table and distributed accordingly in four treatment groups.

Migraine Specific Examination

For the follow up, Patient were provided with a card that contains Name, Age, Sex, Date of follow up and mobile no. of examiner. The patients were told to maintain a Headache diary.

At the follow up visit patients were evaluated for General examination, Systemic examination, primary and secondary outcomes etc.

Clinical Scoring System

Objective sign, symptoms, were observed at baseline, 2 hrs and at 24 hrs. The pain was measured at baseline, at 2 hrs and at 24hrs. The presence and absence of pain was noted at baseline, at 2 hrs and at 24 hrs

Statistical Analysis

All statistical analyses were performed using SPSS software version 23. For all statistical evaluation significance level was taken 95% (P <0.05 was taken to indicate statistical significances). The power of study was 80. The normality of the data was accessed with Shapiro–Wilk test. The analysis population included all the patients who completed the study. Comparisons were made using the Chi square test ($\chi 2$). All tests were two tailed with significance level of 0.05.

OBSERVATION AND RESULTS:

Demographic distribution details

Out of 205 patients, 189 completed the follow up and study consisting of 131 females and 58 males. On group analysis it was found that group 1 consists of 49 patients, group 2 consisted of 46 patients, group 3 consisted of 50 patients and group 4 had 44 patients. Patients who did not reported for follow up were excluded from the study and were not included for the final data analysis

In our study, mean age of presentation was 33.68±8.07. Group wise mean age of presentation was in Group 1 (34.08±7.02, m=13, f=36), Group 2 (35.28±8.79, m=13, f=33), Group 3 (32.74±7.89, m= 17, f=33), Group 4 (32.63±8.54, m=15, f=29). **(Table 1)**

Table 1: Total No Of Patients And Mean Age Of Presentation In Years Along With Standard Deviation (mean ±sd)

Drug Group	Number of Patients	Mean Age+ SD (In Years)
Sumatriptan 100 mg	49	34.08±7.02
Sumatriptan 85 mg + Naproxen 500 mg	46	35.28±8.79
Naproxen 500 mg	50	32.74±7.89
Ergotamine (1 mg) + Caffeine (100 mg) + Paracetamol (250 mg) + Prochlorperazine (2.5 mg)	44	32.63±8.54
Total	189	33.68±8.07

In 72% patients in our study there was positive family history. The baseline characteristics of Migraine was similar in all the groups which were usually unilateral, pulsatile, associated aggravated by strong light

and sound and also physical exercise. The groups were also comparable on basic of general and systemic examinations.

Group 1(n=49) received Sumatriptan (100 mg), Group 2(n=46) received a combination of Sumatriptan (85 mg) and naproxen (500 mg), Group 3(n=50) received Naproxen (500 mg) and Group 4(n=44) received a combination of Ergotamine (1 mg) + Caffeine (100 mg) + Paracetamol (250 mg) + Prochlorperazine (2.5 mg). **(Figure 1)**

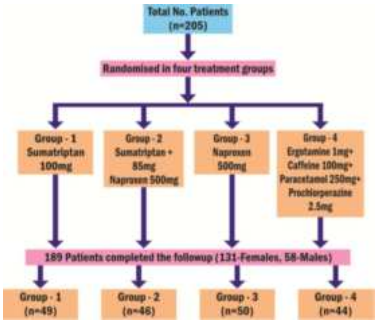

Figure 1: Study plan

On comparing the efficacy of drugs by their ability to terminate the migraine attack within 2 hrs it was observed that there was a significant result when comparing Group 1 and 2 (**p = 0.033**). Another significant result was observed while comparing Group 2 and 3 (**p=0.045**).

Apart from these two comparisons, other group comparisons namely Group 1 and 3, Group 1 and 4, Group 2 and 4 and Group 3 and 4 no significant changes were observed. **(Table 2) (Figure 2)**

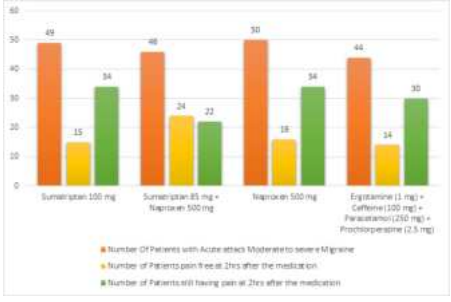

Figure 2: Effect of Different Drugs/Combinations on termination of Acute Attack of Migraine at 2 hours after medication

Table 2: Comparison between different Groups by their ability to terminate the migraine attack within 2 hrs.

Comparison between different Groups	p Value
Sumatriptan vs Sumatriptan + Naproxen	**0.33**
Sumatriptan + Naproxen vs Naproxen	**0.45**
Naproxen vs Ergotamine + Caffeine + Paracetamol + Prochlorperazine	0.98
Sumatriptan vs Ergotamine + Caffeine + Paracetamol + Prochlorperazine	0.9
Sumatriptan vs Naproxen	0.882
Sumatriptan + Naproxen vs Ergotamine + Caffeine + Paracetamol + Prochlorperazine	0.051

While comparing the ability of drugs to cause sustained pain relief observed at 24 hrs. it was observed that there was significant result while comparing group 2 and 3(**p = 0.019**). While comparing other groups namely Group 1 and 3, Group 1 and 4, Group 2 and 4 and Group 3 and 4 no significant changes were observed. **(Figure 3)**

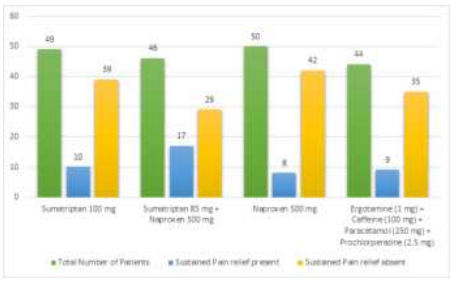

Figure 3: Sustained pain relief observed at 24 hours

DISCUSSION

The present study, an observational, randomized, prospective, open labelled, parallel group trial, which was carried out collectively at Department of Medicine, Swaroop Rani Nehru Hospital and Department of Pharmacology, Moti Lal Nehru Medical college, Prayagraj over a period of one year from 2019 to 2020, compared efficacy of Sumatriptan (100mg), Naproxen (500 mg), a combination of Sumatriptan (85 mg) and naproxen (500 mg),) and a four drug combination of Ergotamine (1 mg) + Caffeine (100 mg) + Paracetamol (250 mg) + Prochlorperazine (2.5 mg).

In the first part of the study, it demonstrated that combination of sumatriptan and naproxen worked significantly better than sumatriptan alone in higher dose in terminating the Migraine attack within 2 hrs.

The combination of sumatriptan and naproxen also worked significantly better than Naproxen alone in terminating the Migraine attack within 2 hrs while the results were having no significant difference while comparing with Ergotamine based 4 drug combination.

There was no other significant difference between the groups in termination of Migraine attack within 2 hrs while comparing

- Higher dose Sumatriptan and Naproxen
- Sumatriptan and Ergotamine based four drug combination
- Naproxen and Ergotamine based four drugs combination

The second part of study consisted the ability of drugs to cause sustained pain relief observed at 24 hrs. It was observed that the combination of Sumatriptan (85 mg) and naproxen (500 mg) worked significantly better in ensuring sustained pain relief as compared to Naproxen (500 mg) alone.

Apart from that there was no significant difference in between the individual groups while ensuring sustained pain relief.

Our findings align with previous research. Brandes et al., in two large, randomized, double-blind studies involving 1461 and 1495 patients, found that the combination of Sumatriptan (85 mg) and Naproxen sodium (500 mg) resulted in a superior 2- to 24-hour sustained pain-free response compared to Sumatriptan monotherapy, Naproxen sodium monotherapy, and placebo (P<.01)[14].Similarly, Law et al. reported that the Sumatriptan-Naproxen combination was more effective than either drug alone or placebo[15].Krymchantowski et al. demonstrated that combining Sumatriptan with Naproxen significantly reduced migraine recurrence rates compared to Sumatriptan monotherapy in patients with high recurrence rates[16]. Smith et al., in a multicentre, randomized, double-blind, placebo-controlled trial, reported that the Sumatriptan-Naproxen sodium group had a significantly higher 24-hour pain relief response compared to Sumatriptan, Naproxen, or placebo (P<.001)[17].

Misra et al. compared Naproxen, Ergotamine, Rizatriptan, and Sumatriptan, finding no significant differences in headache relief 2 hours post-dose[18].Sargent et al. reported that patients receiving Naproxen sodium or Ergotamine had better headache relief at 1 hour compared to placebo, with statistically significant results for Naproxen sodium (p=0.032), but not for Ergotamine (p=0.084) or Naproxen versus Ergotamine (p=0.65) [19].

However, there were several limitations for this study. This study is done over a period of 6 months. So, some dietary and lifestyle parameter changes might have influenced the study. There may be the question of compliance with the use of study drugs. Another limitation of this study might be the individual difference in pain perception for different individuals. The final limitation is the power of the study and also the duration of the Study to ascertain long term effects and safety. Larger groups and longer follow up as needed for acquiring more information

CONCLUSION

By way of conclusion, this study shows that for termination of acute attack of Migraine, the combination of Sumatriptan (85 mg) and naproxen (500 mg) works better than either Sumatriptan (100 mg) or naproxen (500 mg) as Monotherapy but at the same time it is almost

equivalent when compared with combination of Ergotamine (1 mg) + Caffeine (100 mg) + Paracetamol (250 mg) + Prochlorperazine (2.5 mg). It also shows that for producing a sustained pain free relief till 24 hrs, combination of Sumatriptan (85 mg) and naproxen (500 mg) works better than Naproxen(500mg) alone although there is equivalent response with Ergotamine (1 mg) + Caffeine (100 mg) + Paracetamol (250 mg) + Prochlorperazine (2.5 mg) and Sumatriptan (100 mg) as monotherapy.

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