



Comparative Efficacy and Tolerability of Sumatriptan, Ergotamine, Naproxen and Rizatriptan in Moderate to Severe Acute Attack of Migraine

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Abstract

A double-blind, randomized, parallel study was done to compare sumatriptan, ergotamine, naproxen and rizatriptan in 40 outpatients treating a single migraine attack of moderate to severe intensity. Among these groups, significantly more number of patients had headache relief at 2 hours postdose in naproxen and rizatriptan group as compared to ergotamine. Naproxen, rizatriptan and sumatriptan were better than ergotamine in causing freedom from the associated symptoms of nausea, vomiting, photophobia and phonophobia at 2 hour postdose. Naproxen, rizatriptan and sumatriptan were also efficacious in causing functional normalization at 2 hours postdose as compared to ergotamine. The overall results of the study suggest that naproxen is as efficacious as triptan group of drugs but better than ergotamine group in treatment of moderate-severe acute migraine attack. It is more cost effective than triptans and also a well tolerated drug

Key Words

Migraine, Sumatriptan, Ergotamine, Naproxen, Rizatriptan

Introduction

Migraine is a common multifactorial, neurovascular disorder, typically presenting as recurrent disabling attacks of headache, lasting for 4 to 72 hours, associated with nausea, photophobia, phonophobia and transient neurological aura symptoms. WHO recognizes migraine together with quadriplegia, dementia and psychosis as one of the most disabling disorders (1, 2). For the treatment of acute migraine, the most commonly prescribed drugs belong to non-steroidal anti-inflammatory drugs (NSAIDs) and 5-hydroxytryptamine (5-HT) agonist groups. Currently, triptans are considered as specific antimigraine drugs and are evolving as first choice. Still in many countries, ergotamine and NSAIDs are commonly prescribed for the indication and also in many clinical trials NSAIDs have shown equivalent efficacy as triptans for moderate to severe acute migraine (3-13). Against this background, this study aims at evaluating efficacy and safety of commonly prescribed drugs for moderate to severe acute migraine: rizatriptan, sumatriptan, ergotamine compound and naproxen.

Materials & Methods

The present study was a double blind parallel group study. Patients aging between 16 to 65 years with established diagnosis of migraine with or without aura were included in the study. *International Headache Society Diagnostic Criteria* were used to define the intensity of migraine as moderate (pain influencing patient's job performance, but he does not miss work) or severe (pain influencing work, school & social situations and he loses time for activities) (14,15). A written informed consent was taken from all the patients. The patients with a history of basilar, ophthalmoplegic or hemiplegic migraine, with organic or structural brain lesion, ischemic heart disease, Prinzmetal angina, WPW syndrome, cardiac conduction defect or arrhythmias, uncontrolled hypertension, were excluded. Other exclusion criteria were patients currently on prophylactic medication, pregnancy or amenorrhea, severe renal or hepatic disease and severe vomiting requiring parenteral drug administration. A total of 62 patients were screened, out of which 54 patients fulfilled the inclusion criteria and

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were recruited to study protocol (*Fig 1*). Out of these, 11 patients chose not to be treated owing to various reasons. The remaining 43 patients were randomly divided using random number table into 4 groups (according to oral medication given to them). The blinding was done by giving identical packets containing the respective medication. The medications were either 1 of the following 4, coded as A, B, C, and D: Naproxen (500 mg), Sumatriptan (50mg), Rizatriptan (10mg) and Ergotamine tartrate (2mg) + caffeine (100mg) + cyclizine HCl (50mg).

The patients were advised to take single dose of study drug during moderate to severe migraine attack. The patients were instructed to note the headache severity, functional disability and associated symptoms as nausea/vomiting / photophobia / phonophobia at 0 hour (baseline) and then after 1, 2, 12, and 24 hours post dose of study. Rescue medication (Piroxicam-20mg) was advised only if headache persisted beyond 2 hours or recurred. The patients were provided with a questionnaire to note above-mentioned details and present it to the investigator within 48 to 72 hours of migraine attack. The questionnaire was cross-checked and further verified by the investigator to ensure proper and complete information. The assessment of a single migraine attack was done. Also the assessment of quality of life (QOL) at baseline and 24 hours postdose of study drug were done by Migraine specific QOL questionnaire (15). Three patients were found to be protocol violators and were excluded from the efficacy population (*Fig 1*). Forty patients completed the study; the efficacy end points in them were statistically analyzed.

The primary end point of the study was the proportion of patients with headache relief within 2 hours of intake of study drug. Headache relief was defined as relief from severe (grade 3) or moderate (grade 2) pain to mild (grade 1) or no (grade 0) pain. Secondary end points were proportion of patients with "sustained pain relief" within 24 hours after study drug, and proportion of patients with freedom from associated symptoms and functional disability at 2 hours post-dose. Sustained pain relief was defined as the proportion of patients having initial headache relief at 2 hours post-dose and with no recurrence of moderate to severe headache during 2-24 hours. Also analyzed was the proportion of patients having headache relief at 1 hour post-dose. Headache and associated symptoms were graded on a 4-point scale. The adverse drug reactions within 24 - 48 hours study period were assessed by the investigator (14-16).

Cost-effectiveness was defined as the cost to reduce headache severity by 1 unit. It was measured by the

ratio of cost of treatment to outcome. The outcome was measured by reduction in mean headache severity at 2 hours postdose compared to baseline headache severity.

The comparison of overall improvement in QOL 24 hours postdose of study drug to QOL during acute migraine attack (at baseline) was done by using Migraine specific QOL questionnaire- 24 hours. (15)

Chi-square test was used to analyze study end-points between the 4 groups. Fischer's exact test was used for inter-group analysis of study end points. The individual drug significance was analyzed by paired t-test. The mean improvement in QOL from baseline to 24 hours postdose by various study drugs was analyzed by unpaired t-test.

Results

The baseline demographic profile of patients in all study groups was similar. The mean age of patients was 32.6 ± 2.57 years. There was a female preponderance of disease especially in middle age; 27 out of 40 patients were females. A positive family history was present in 68% patients in our study, suggesting the familial predisposition of the disease. The mean duration of illness in our patients was 5.69 ± 0.98 years. The mean frequency of attacks was 3.65 ± 0.57 per month. The baseline headache characteristics of patients in all study groups were similar. Most of the headache attacks were unilateral at onset, pulsatile in nature and aggravated with physical exertion. The migraine attacks were associated with nausea, vomiting, photophobia, phonophobia, aura and functional disability. The most common accompanying symptoms were photophobia, phonophobia and nausea. Aura was the least common accompanying symptom. Functional disability was present in all patients during migraine attack.

Naproxen and rizatriptan were significant in causing headache relief at 2 hours postdose as compared to ergotamine ($p < 0.05$ compared to ergotamine) (*Fig 2*). Naproxen, rizatriptan and sumatriptan were better than ergotamine in causing freedom from the associated symptoms of nausea, vomiting, photophobia and phonophobia at 2 hours postdose. Naproxen, rizatriptan and sumatriptan were also efficacious in causing functional normalization at 2 hours postdose as compared to ergotamine. Recurrence of headache was seen in 2 patients in the rizatriptan group within 24 hours of postdose after an initial headache response. Naproxen was significant than ergotamine and better than triptans in causing sustained pain relief within 24 hours postdose. Analysis of more stringent efficacy parameter revealed superiority of naproxen in causing headache relief at 1 hour postdose compared to ergotamine (*Fig 2*). The mean improvement in QOL at 24 hours postdose was more with naproxen and rizatriptan group as compared to



Table 1: Side Effects of Study Drugs Within 24-48 Hours of Uptake

	Group A (n=10)	Group B (n=10)	Group C (n=10)	Group D (n=10)	Total (n=40)
Dizziness	0	2	0	0	2
Gastrointestinal discomfort	3	0	0	0	3
Metallic Taste	0	1	1	0	2
Nausea	0	1	1	3	5
Paresthesias	0	0	1	2	3
Muscle cramps	0	0	0	0	0
Rashes	0	0	0	0	0
Chest pain	0	0	0	0	0
Total	3	4	3	5	15

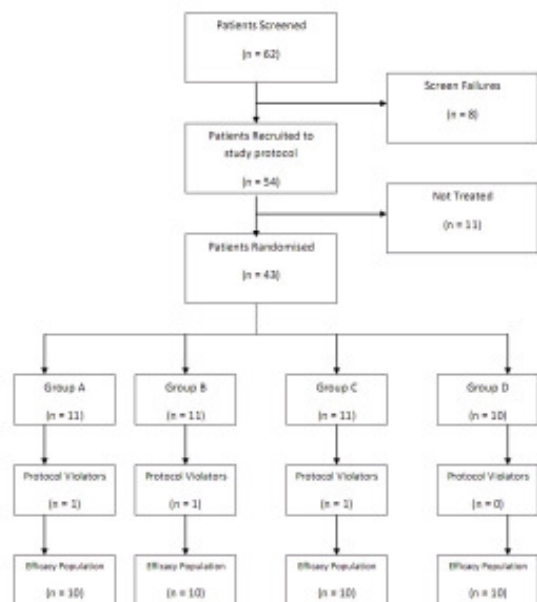


Fig 1. Study Enrollment & Completion Diagram

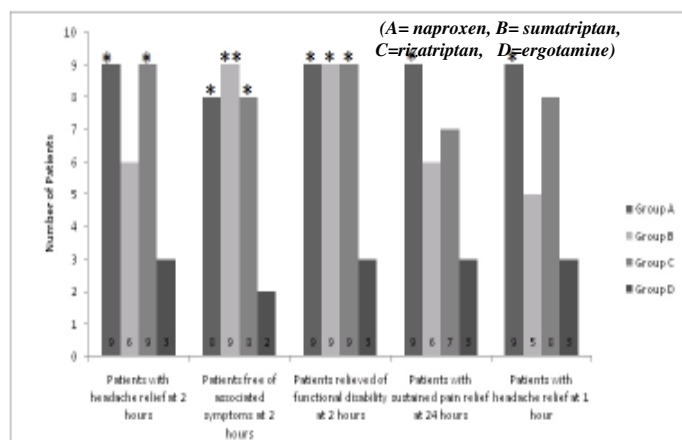


Fig 2. Analysis of Study End-Points (* $p < 0.05$ vs group D; ** $p < 0.01$ vs group D, + $p < 0.05$ vs group B, + $p = 0.05$ vs group D)

ergotamine ($p < 0.05$ compared to ergotamine). The side effects were transient and mild in intensity. Overall frequency of adverse effects was 37.5%. The maximum incidence was of nausea, gastrointestinal discomfort and paraesthesias. Maximum incidence of side effects was seen in the ergotamine group (Table 1). The most cost-effective drugs were ergotamine and naproxen. Sumatriptan was the least cost effective (Fig 3). The overall results of the study suggest that naproxen is as efficacious as triptan group of drugs but better than ergotamine group. It is more cost effective than triptans and also a well tolerated drug.

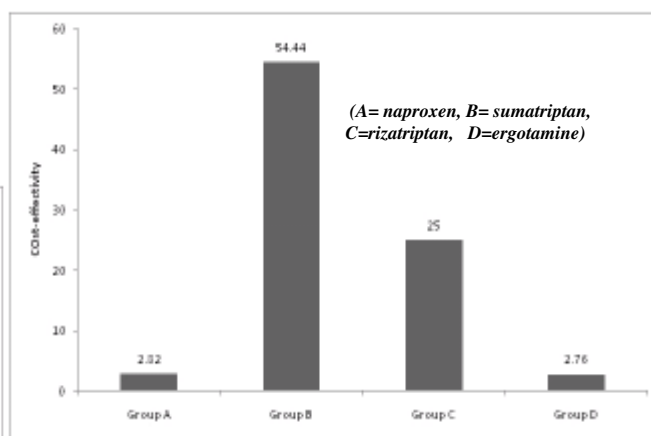


Fig 3. Cost-Effectiveness of Study Drug (Expressed as Cost to Reduce Headache Severity by 1 unit at 2 Hours)

Discussion

This double blind randomized parallel group study compares efficacy and safety of naproxen, ergotamine compound, rizatriptan and sumatriptan. The trial demonstrated equivalent efficacy of naproxen and triptans in attainment of headache relief at 2 hours postdose. Naproxen and triptans were also comparable in causing freedom from nausea, vomiting, photophobia, phonophobia and functional disability. Both these drugs were superior to ergotamine in attainment of various efficacy end points.

Ergotamine and triptans are non-selective and selective 5HT_{1B/1D} agonists, respectively. They cause cranial vasoconstriction, inhibition of serotonergic neurons mediated pain neurotransmission and inhibit release of vasoactive peptides causing vasodilatation and neurogenic inflammation (17,18). Naproxen not only acts as an analgesic and anti-inflammatory drug, causing symptomatic relief, but also blocks neurogenic dural



plasma extravasation and terminal sensitization of brain stem caused by calcitonin gene related peptide mediated vasodilatation.(3,19-20). This explains similar efficacy of naproxen as that of triptans. These drugs are commonly prescribed for treatment of moderate to severe acute migraine. The introduction of triptans in migraine treatment was apparently a revolution. Triptans have shown efficacy over placebo in various clinical trials and are considered as migraine specific first line therapy. In our study triptans and naproxen show little difference in terms of efficacy, similar to other head-head comparative trials of triptans versus NSAIDs (3-13). Ergotamine was found to be inferior to both naproxen and triptans in our study, which is similar to results in the past (21-24). This may be due to low oral bioavailability of ergotamine (18).

Naproxen was better than triptans and significantly superior to ergotamine in attainment of sustained pain relief at 24 hours. Naproxen showed highest sustained headache relief because of its high initial headache response and no recurrence due to long duration of action ($t_{1/2}$ =14 hours). Headache recurrence is a problem with triptans having short half-life as sumatriptan and rizatriptan, it has been seen in 15-40% patients clinically (25, 26).The stringent efficacy end point was also secondarily analyzed that is headache relief at 1 hr. The headache relief rates correspond to t-max of the drug. These were higher for naproxen and rizatriptan. For naproxen t-max is 1.5 hr, but some studies have shown analgesic effect to come as soon as 1 hr (20, 27). Among triptans rizatriptan has quickest onset of action, t-max=1hr (28,29). Ergotamine t-max is 0.5-3 hours, but its oral bioavailability is very low (18,30).

Moderate to severe migraine attacks have a negative impact on functioning and QOL including physical, emotional and social aspects of daily life (31). The improvement in QOL at 24 hours in naproxen and rizatriptan was superior to ergotamine at 24 hours. This correlates with other efficacy parameters of our study as it is a composite scoring scale. All the study drugs were well tolerated. The maximum incidence of side effects was seen in the ergotamine group; nausea and paraesthesias being most common. This is because of nonselective action of ergotamine acting on chemotrigger zone and vasoconstrictive nature respectively (18, 30). In the naproxen group, gastrointestinal discomfort and dyspepsia were reported, due to inhibition of gastroprotective cyclo-oxygenase-1 enzyme (20).

The prevalence of migraine is highest among adults aged 25 to 55 years, the peak years of work productivity. The annual economic burden of migraine is estimated to be comparable to that of patients currently on medication

of diabetes (32). There was a huge difference in cost effectiveness between ergotamine, naproxen and triptans. Most cost effective drugs were naproxen and ergotamine. Sumatriptan was the least cost effective. This is the major disadvantage with triptans as compared to other antimigraine drugs.

A small sample size and evaluation of single attack were the main limitations of this study. Also, pain relief was based on subjective evaluation by the patients, which is an inherent limitation of trials evaluating migraine. Keeping all these limitations in view, larger studies evaluating multiple attacks in the same patient are warranted in the future.

Conclusion

The overall results of the study suggest that the efficacy of naproxen for all the end points and improvement in QOL is equivalent to that of triptans. Naproxen was as well tolerated as, if not better than, the triptans. Naproxen is much more cost-effective than the triptans. Also, naproxen has long duration of action, so attainment of sustained headache relief is better compared to triptans. Considering all these facts, we suggest that naproxen be used as an alternative drug for treatment of moderate-to-severe migraine attack.

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