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Rizatriptan *vs.* ibuprofen in migraine: a randomised placebo-controlled trial

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Abstract The objective of this study was to compare the efficacy of rizatriptan and ibuprofen in migraine. The study was a randomised placebo-controlled trial in a tertiary care teaching hospital. Migraine patients with <8 attacks/months were included. One hundred and fifty-five migraine patients were randomised to rizatriptan 10 mg (53), ibuprofen 400 mg (52) and placebo (50). Efficacy was assessed by headache relief, and headache freedom at 2 h and 24 h. Two-hour headache relief was noted in 73% in rizatriptan, 53.8% in ibuprofen and 8% in placebo groups. Headache freedom was achieved in 37.7% in rizatriptan, 30.8% in ibuprofen and 2% in placebo groups. Rizatriptan was superior to ibuprofen and placebo in relieving headache at 2 h but not at 24 h. Side effects were noted in 9 patients in rizatriptan, 8 in ibuprofen and 3 in placebo, all of which were nonsignificant. Rizatriptan and ibuprofen are superior to placebo. Rizatriptan is superior to ibuprofen in relieving headache, associated symptoms and functional disability.

Keywords Migraine • Rizatriptan • Acute attack • Randomised controlled trial • Treatment

Introduction

For treating acute migraine attacks, a number of drugs are used, including ergot alkaloids, nonsteroidal anti-inflammatory drugs (NSAIDS), acetaminophen and triptans. Both Cox I and Cox II inhibitors have been investigated and found to be effective in migraine [1, 2], however rofecoxib has been withdrawn due to toxicity [3]. The reported efficacy of NSAIDS is 42%–72% [1, 4–7]. NSAIDS are in use because of their predictable response, low cost and well known side-effect profile. Triptans are a new class of drugs, which are 5HT1B-D agonists, quick acting and have low gastrointestinal toxicity. Amongst the triptans, oral rizatriptan has been reported to be more effective than sumatriptan, naratriptan and zolmitriptan [8]. In a cross-over study, rizatriptan was found to be superior to ergotamine and caffeine combination in relieving acute migraine attack [9]. The decision to choose a new drug is based not only on its efficacy compared to placebo but also its relative advantage over other available drugs. There is no study comparing rizatriptan with other NSAIDS. We therefore report the results of a randomised placebo-controlled trial (RCT) comparing rizatriptan with ibuprofen and placebo.

Subjects and methods

This study was conducted in a tertiary care teaching hospital during 2004–2006 and was duly approved by the local ethics committee. The patients were recruited from out patient service of the Neurology Department. Migraine patients above the age of 12 years were diagnosed on the basis of International Headache Society criteria [10]. Patients with mild (grade I) headache, headache with recurrent vomiting or more than 8 attacks per month, pregnant or lactating mothers, and those on oral contraceptives, or with a history of drug allergy, intractable hypertension, renal or hepatic failure, coronary artery disease, pulmonary, psychiatric or other neurological diseases were excluded. The patients were subjected to detailed medical history and physical examination as per fixed protocol. The patients were randomised into rizatriptan, ibuprofen and placebo using computer-generated random numbers. Randomisation was done by one investigator and evaluation by another. The patients were asked to record severity of headache, functional disability and associated symptoms such as nausea, vomiting, phonophobia, photophobia and allodynia before and 2 h after medication in a headache diary. Relapse of headache within 24 h was also noted. Headache relapse was defined as occurrence of moderate to severe headache within 24 h of dosing in patients who initially had relief of pain 2 h after medication. The severity of headache was graded on a 0–III scale (0=normal, grade I=mild, grade II=moderate and grade III=severe). Functional disability was graded as 0=normal, I=daily activity mildly impaired, II=daily activity moderately impaired, III=daily activity severely impaired and IV=inability to perform daily activities requiring bed rest [8]. The severity of associated symptoms of nausea, vomiting, photophobia and phonophobia were also graded on a 0–III scale: 0=normal, I=mild, II=moderate, III=severe. The patients were advised to take study medication (rizatriptan 10 mg, ibuprofen 400 mg or placebo) if the headache was moderate to severe provided in identical packets. Rescue medication piroxicam 20 mg was advised if moderate to severe headache persisted 2 h after initial medication.

The patients were subjected to blood counts, urinalysis, blood sugar, serum creatinine, bilirubin, serum transaminases and electrocardiogram. Any side effect up to 24 h after medication was recorded.

Efficacy measurement

Efficacy of drug was evaluated at the 1-month follow-up visit or after 2 or more attacks, which were documented in the headache diary. The primary end-point was percentage of patients having pain relief at 2 h. Pain relief was considered if severity of headache was reduced to grade I or 0. The secondary end-point was percentage of patients with relief of associated symptoms, functional disability at 2 h and pain freedom at 24 h.

Sample size calculation and statistics

The calculated sample size was 156, taking α=0.05, critical difference between the drugs 15% and standard deviation (SD) 2. The power of test as evaluated for Mann-Whitney *U*-test was 78.62%. The baseline characteristics between groups were compared by independent t, χ^2 and Fisher's exact tests. The efficacy of drugs between the groups was analysed by Mann–Whitney U-test and within the same group by Wilcoxon signed ranked test. The numbers of patients with headache relief at 2 h and relapse within 24 h were compared by χ^2 test.

Results

During the study period 174 migraine patients fulfilled the inclusion criteria. Nine patients were excluded due to lack of consent. Fifty-seven patients were randomised to rizatriptan, 55 to ibuprofen and 53 to placebo. Four patients in rizatriptan and 3 each in ibuprofen and placebo were lost from follow-up (Fig. 1). Our results therefore are based on 155 migraine patients whose age ranged between 16 and 58 (mean 30.5) years, 106 of whom were females. All the patients had migraine without aura. The duration of migraine ranged between 6 and 260 (mean 63.2) months. The mean frequency of migraine attacks was 4.4 (range 2–8) per month. Eighty-seven patients had moderate and 68 severe headache. The mean headache score was 2.44±0.50, associated symptoms score 2.08±0.29 and functional disability score 2.36±0.73. Fifty-three patients were randomised to rizatriptan, 52 ibuprofen and 50 placebo groups. The demographic and clinical variables of these groups were not significantly different (Table 1).

Efficacy

Two-hour headache relief was achieved by rizatriptan in 39 (73%), ibuprofen in 28 (53.8%) and placebo in 4 (8%) patients. Two-hour headache freedom was achieved by rizatriptan in 20 (37.7%), ibuprofen in 16 (30.8%) and placebo in 1 (2%) patients. Rizatriptan was significantly better than ibuprofen in relieving headache (p=0.0001) but not in achieving pain freedom (p=0.38). The headache score at 2 h compared to baseline was significantly greater in rizatriptan (p=0.0001) and ibuprofen (p=0.0001). Functional disability and associated symptoms were also significantly reduced at 2 h in both rizatriptan and ibuprofen groups. However in the placebo group, headache severity and functional disability were significantly increased at 2 h (Table 2).

Comparing the efficacy between the groups revealed significant improvement in headache score, associated symp-

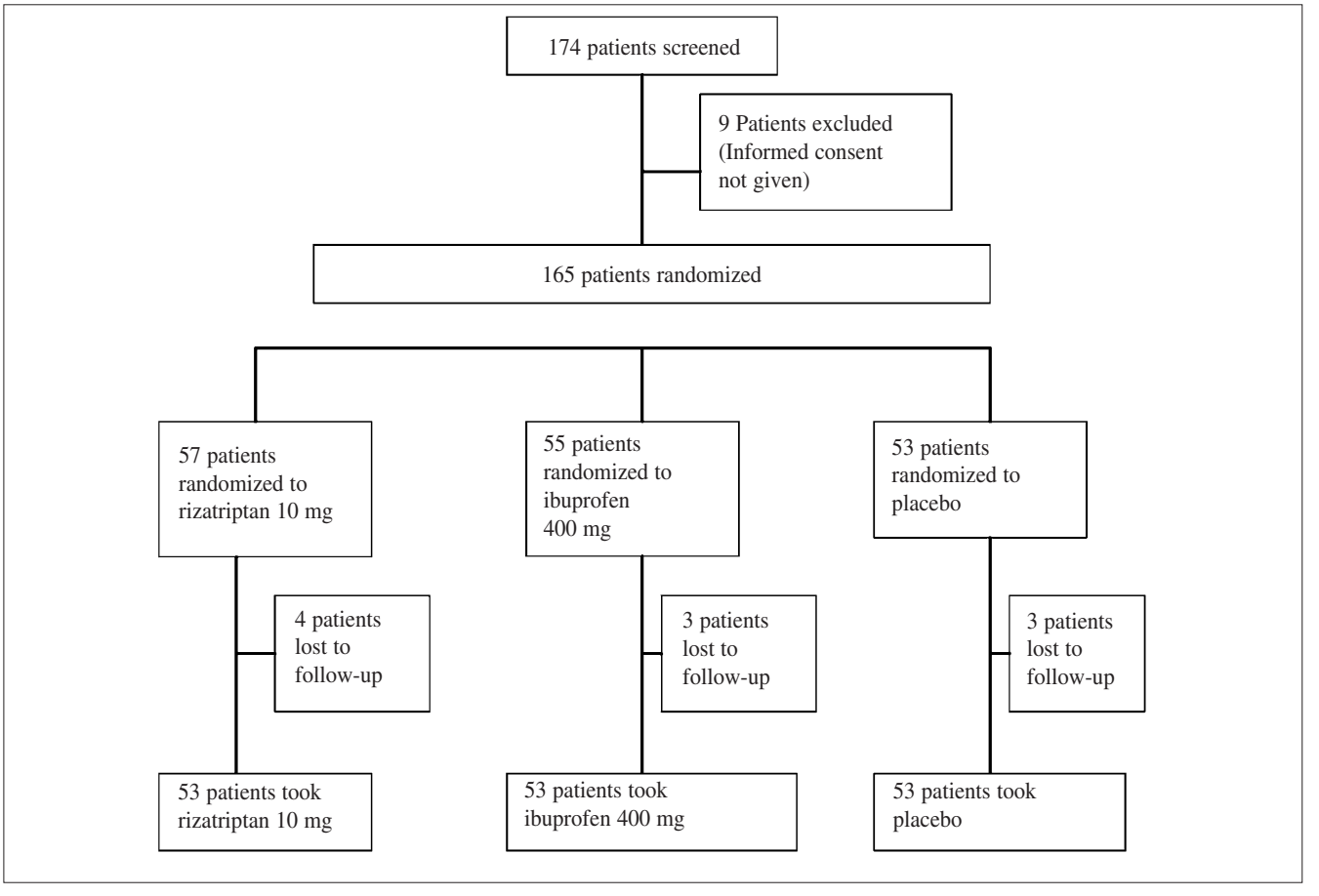

Fig. 1 Flow chart showing randomization of migraine patients

Table 1 The comparison of demographic and clinical variables of migraine patients between study and control groups, which were not significant

Variables	Rizatriptan (n=53)	Ibuprofen (n=52)	Control (n=50)
Age (yrs)	29.15±8.7	30.5±10.6	31.78±9.9
Females	36	38	40
Number of attacks	4.6±.13	4.2±1.2	4.5±1.4
Duration (months)	60.8±60.7	65.7±68.3	63.1±57.0
Family history	15	17	8
Nausea	53	51	43
Vomiting	47	46	46
Photophobia	53	52	50
Phonophobia	53	52	50
Functional disability			
I	3	10	4
II	28	21	22
III	21	17	23
IV	1	4	1
Severity of headache			
Moderate	28	28	31
Severe	25	24	19
Duration of attack (hours)	17.0±10.3	13.6±8.8	14.8±10.9

toms and functional disability both in rizatriptan and ibuprofen compared to placebo. However the difference between rizatriptan and ibuprofen was not significant (p=0.09). Rizatriptan resulted in significant relief in associated symptoms and functional disability and insignificant improvement in headache score compared to ibuprofen (Table 3). Twenty-four-hour headache relapse in the patients who responded at 2 h was noted in 6 (15.38%) in rizatriptan, 5 (17.85%) in ibuprofen and 1 (25%) in placebo groups. This difference was not significant (p=0.87). A significantly higher number of patients needed rescue medication (piroxicam 20 mg dispersible) in the placebo group (46) compared to the rizatriptan (14) and ibuprofen (24 patients; p<0.0001) groups. Requirement of rescue medication was also significantly higher in ibuprofen compared to rizatriptan (p=0.04).

In our study 20 patients developed side effects: 9 in rizatriptan (palpitation 6, somnolence 2 and gastric discomfort 1), 8 in ibuprofen (gastric discomfort in all) and 3 in the placebo group (gastric discomfort in all). The side effects were mild to moderate and could be easily controlled without any protocol violation.

Discussion

Our study reveals that rizatriptan and ibuprofen were superior to placebo in relieving pain, associated symptoms and functional disability at 2 h compared to placebo. These are in agreement with the earlier studies in which rizatriptan 10 mg was superior to placebo [11]. Efficacy of rizatriptan in relieving headache has been reported to be from 52% to 67.3% and 2-h pain freedom 26% to 49%. In our study rizatriptan resulted in headache relief in 73% and headache freedom in 37.7% patients. Ibuprofen resulted in headache relief in 53.8% and

Table 2 Efficacy of rizatriptan, ibuprofen and placebo in patients with migraine

Drugs	Before treatment (mean±SD)	2 hour after treatment (mean±SD)	Z value	p
Rizatriptan (53)				
Headache score	2.47±0.50	1.02±1.03	–5.85	0.0001
Functional disability score	2.38±0.63	1.04±0.98	–5.75	0.0001
Associated symptom score	2.13±0.34	0.85±0.82	–6.25	0.0001
Ibuprofen (52)				
Headache score	2.44±0.54	1.35±1.14	–5.03	0.0001
Functional disability score	2.29±0.87	1.27±1.10	–5.57	0.0001
Associated symptom score	2.06±0.24	1.13±0.79	–5.48	0.0001
Placebo (50)				
Headache score	2.38±0.49	2.42±0.67	–2.07	0.04
Functional disability score	2.22±0.68	2.28±0.70	–2.33	0.02
Associated symptom score	2.04±0.29	1.70±0.71	–3.00	0.0003

Table 3 Comparison of efficacy of rizatriptan, ibuprofen and placebo in acute migraine attack

Difference in score	Rizatriptan Vs Ibuprofen	Rizatriptan Vs placebo	Ibuprofen Vs placebo
Headache	1.45±0.93 vs 1.12±1.08	1.45±0.93 vs 0.16±0.51	1.12±1.08 vs 0.16±0.51
Z/p value	–1.69/0.09	–6.68/0.0001	–5.10/0.0001
Associated symptoms	1.25±0.83 vs 0.90±0.85	1.25±0.83 vs 0.26±0.66	0.90±0.85 vs 0.26±0.66
Z/p value	–2.06/0.04	–5.82/0.0001	–4.33/0.0001
Functional disability	1.34±0.90 vs 0.98±0.94	1.34±0.90 vs 0.14±0.40	0.98±0.94 vs 0.14±0.40
Z/p value	–21.3/0.03	–6.78/0.0001	–5.38/0.0001

headache freedom in 30.8% patients. The efficacy of ibuprofen in earlier studies has been reported to be 42%–70% [4, 7, 12, 13].

On comparing with ibuprofen, rizatriptan was better in relieving pain, associated symptoms and functional disability at 2 h. Rizatriptan has been compared with other triptans and is reported to be superior to sumatriptan, zolmitriptan and naratriptan in 2-h pain relief and 24-h headache freedom [8]. Acetaminophen, aspirin and NSAIDS in migraine have been found to be effective and well tolerated in adults and children [4, 14]. In childhood migraine, ibuprofen has been found to be superior to acetaminophen [4]. There is however no study comparing the relative efficacy of rizatriptan and NSAIDS. Triptans, especially sumatriptan, have been compared with naproxen, indomethacin, aspirin and ibuprofen [14–16]. In an RCT, ibuprofen resulted in headache relief in 62.5%, sumatriptan in 55.8% and headache freedom was 33.2% and 37.1% patients respectively, which were not significant [14]. In our study, rizatriptan resulted in significant pain relief, reduction in associated symptoms and functional disability compared to ibuprofen. Gastrointestinal side effects were more common with ibuprofen and palpitations with rizatriptan; however, the side effects were not severe enough to warrant discontinuation in any patient.

Our study is limited by the relatively small number of patients. As the study was conducted in a single centre, there is homogeneity in patient selection and low inter-rater variability. Efforts were made to blind the randomising and evaluating investigators and medication was provided in identical packets to eliminate bias.

Both rizatriptan and ibuprofen are superior to placebo in aborting acute migraine attack. Rizatriptan 10 mg is superior to ibuprofen in relieving headache, associated symptoms and functional disability.

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