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Rizatriptan versus rizatriptan plus rofecoxib versus rizatriptan plus tolfenamic acid in the acute treatment of migraine

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Abstract

Background: Rizatriptan is an effective and fast acting drug for the acute treatment of migraine. Some nonsteroidal anti-inflammatory drugs (NSAID) have also demonstrated efficacy in treating migraine attacks. There is evidence that the combination of a triptan and a NSAID decreases migraine recurrence in clinical practice. The primary aim of this randomized open label study was to assess the recurrence rates in migraine sufferers acutely treated with rizatriptan (RI) alone vs. rizatriptan plus a COX-2 enzyme inhibitor (rofecoxib, RO) vs. rizatriptan plus a traditional NSAID (tolfenamic acid, TO). We were also interested in comparing the efficacy rates within these three groups.

Methods: We assessed 45 patients from a headache clinic in Rio de Janeiro (35 women and 10 men, ages 18 to 65 years, mean 37 years). Patients with IHS migraine were randomized to one out of 3 groups, where they had to treat 6 consecutive moderate or severe attacks in counterbalanced order. In group 1, patients treated the first two attacks with 10 mg RI, the third and fourth attacks with RI + 50 mg RO and the last attacks with RI + 200 mg of TA. In group 2, we began with RI + TA, followed by RI, and RI + RO. Group 3 treated in the following order: RI + RO, RI + TA, RI alone. The presence of headache, nausea and photophobia at 1, 2 and 4 hours, as well as recurrence and side effects were compared.

Results: A total of 33 patients finished the study, treating 184 attacks. The pain-free rates at 1 hour were: RI: 15.5%; RI + RO: 22.6%; RI + TA: 20.3%(NS). Pain-free rates at 2 h were: RI: 37.9%; RI + RO: 62.9%, and RI + TA: 40.6% ($p = 0.008$ for RI vs. RI + RO; $p = 0.007$ for RI + RO vs. RI + TA, NS for RI vs RI + TA). At 4 h, pain-free rates were: RI: 69%; RI + RO: 82.3%; RI + TA: 78.1% (NS for all comparisons). The combination of RI + RO was superior to RI and to RI + TA in regard of the absence of nausea and photophobia at 4 hours. Recurrence (after being pain-free at 2 h) was observed in 50% of patients treated with RI, in 15.4% of those treated with RI + RO, and in 7.7% of those treated with RI + TA.

Conclusions: Despite the methodological limitations of this study, the combination of RI and RO revealed a higher response rate at 2 hours. Recurrence was also clearly decreased with both combinations in relation to the use of RI alone. Controlled studies are necessary to provide additional evidence.

Background

Triptans are effective drugs for the acute treatment of migraine, and the drugs of choice for disabling migraine attacks [1-4]. Rizatriptan (RI) is a fast acting triptan with good efficacy at 2 hours. Placebo-controlled studies for the 10 mg RI tablet found a 2-hour therapeutic gain ranging from 27% to 40%, with headache relief at 2 hours ranging from 70 to 77% and a pain-free response at 2 h ranging from 40% to 44% (Placebo response ranging from 2 to 10%). The recurrence rate for the 10 mg tablet ranges from 30% to 47% [5-7]. Although being a very effective triptan, incomplete relief and recurrence may cause frustration to an expressive number of patients [8,9].

Some non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid, ibuprofen, diclofenac, naproxen sodium, mefenamic acid, tolfenamic acid and lysine clonixinate have also demonstrated efficacy in the acute treatment of migraine [10-12]. The combination of a triptan and a NSAID seems to decrease headache recurrence and increase the efficacy, being an interesting alternative in clinical practice to selected patients [13-15]. Rofecoxib (RO) is a long-acting (half-life of 17 hours) member of a new class of NSAIDs, which selectively inhibits the COX-2 enzyme, being therefore better tolerated with regard to gastrointestinal side effects [16,17]. Its combination with RI seems to decrease the headache recurrence and to increase the therapeutic gain at 2 hours [15]. Tolfenamic acid (TA) is a traditional NSAID with proven efficacy in the acute treatment of migraine. Its combination with sumatriptan also decreases headache recurrence in clinical practice [12,13].

Accordingly, in this randomized open label study we compared RI alone vs. RI plus RO vs. RI plus TA in the acute treatment of moderate or severe migraine attacks.

Methods

Forty-five patients from a private headache clinic in Rio de Janeiro, Brazil, (35 women and 10 men, ages from 18 to 65 years, with a mean of 37 years) were enrolled. All patients received a diagnosis of migraine according to the criteria proposed by the IHS (International Headache Society) [18], and were randomized to one out of 3 groups, where they treated 6 consecutive attacks in counterbalanced order. To be included, subjects had to present 2-8 migraine attacks in the previous three months, use medications to treat their attacks and to be on stable dose of preventive treatments other than NSAID for more than one month. Patients with a history of active peptic disease as those receiving treatment for any other major medical or psychiatric conditions were excluded. The past history of taking any of the 3 study medications was not considered for inclusion/exclusion.

Patients randomized to Group 1 treated their first two consecutive moderate or severe attacks with 10 mg RI, the third and fourth consecutive attacks with RI + 50 mg RO and the last two consecutive attacks with RI + 200 mg of TA. In group 2, we began with RI + TA, followed by RI, and RI + RO. Patients in group 3 treated in the following order: RI + RO, RI + TA, and RI alone. This method of randomization allowed each group to start and to finish with a different drug scheme. The Institutional Review Board of the University Federal Fluminense at Rio de Janeiro approved the study and all patients were informed that the purpose of this study was to test potential differences in efficacy and recurrence and gave informed consent.

We assessed the following endpoints: Pain-free rates at 1, 2 and 4 hours; recurrence at 24 hours (defined as the recurrence of headache after being pain-free at 2 hours); presence of nausea and photophobia at 1, 2, and 4 hours; side effects at any time point after receiving the study drug. Endpoints were assessed through an objective written report to be filled out by each patient during each of the treated attacks, and were also derived from headache calendars. Data assessing previous habits regarding the patient's timing of acute treatment of migraine attacks were not collected. All patients were informed that treating attacks at mild severity would be considered protocol violations and would not be used to draw conclusions.

Data were analyzed separately for each time point (hour 1, 2, or 4). A logistic regression model was built to control for efficacy of treatment, sequence of treatment and attack number. The method of generalized estimating equations was used to account for the correlation within subjects. Nausea and photophobia were analyzed using just those attacks where the symptom was present at baseline.

Results

Thirty-three patients completed the study and treated a total of 184 moderate or severe migraine attacks. Fourteen attacks (6 patients), treated when pain was mild, were not included in the analysis. Four patients of each of the groups did not fill out the reports adequately and/or did not follow the correct order of taking study drugs. Baseline intensity is summarized in Table 1. Group 1 treated 58 attacks (40 moderate, 18 severe), group 2 treated 62 attacks (44 moderate, 18 severe) and group 3 treated 64 attacks (41 moderate, 23 severe) (NS).

The pain-free rates at 1 hour were: RI: 15.5%; RI + RO: 22.6%; RI + TA: 20.3% (NS). Pain-free rates at 2 h were: RI: 37.9%; RI + RO: 62.9%, and RI + TA: 40.6% ($p = 0.008$ for RI vs. RI + RO; $p = 0.007$ for RI + RO vs. RI + TA, NS for RI vs RI + TA). At 4 h, pain-free rates were: RI: 69%; RI + RO: 82.3%; RI + TA: 78.1% (NS for all comparisons) (Table 2).

Table 1: Number of attacks by treatment and baseline intensity

	RI		RI + RO		RI + TA	
	n	%	n	%	n	%
Moderate	40	69.0	44	71.0	41	64.1
Severe	18	31.0	18	29.0	23	35.9
Total	58	100.0	62	100.0	64	100.0

RI: rizatriptan; RO: rofecoxib; TA: tolfenamic acid

Table 2: Pain free rates at consecutive timepoints.

Treatment	1 hour n/N (%)	2 hours n/N (%)	4 hour n/N (%)
RI	9/58 (15.5%)	22/58 (37.9%)	40/58 (69%)
RI + RO	14/62 (22.6%)	39/62 (62.9%)	60/62 (82.3%)
RI + TA	13/64 (20.3%)	26/64 (40.6%)	50/64 (79.1%)
P value	NS for all comparisons	P = 0.008 for RI vs RI + RO P = 0.009 for RI vs RI + TA NS for RI + RO vs RI + TA	NS for all comparisons

RI: rizatriptan; RO: rofecoxib; TA: tolfenamic acid; n: number of attacks with nausea; N: number of treated attacks.

Table 3: Absence of nausea at consecutive timepoints.

Treatment	1 hour n/N (%)	2 hours n/N (%)	4 hour n/N (%)
RI	7/27 (25.9%)	12/27 (44.4%)	17/27 (63%)
RI + RO	18/28 (35.7%)	20/28 (71.4%)	24/28 (85.7%)
RI + TA	5/25 (20%)	17/25 (68%)	22/25 (88%)
P value	NS for all comparisons	P = 0.01 for RI vs RI + RO P = 0.09 for RI vs RI + TA NS for RI + RO vs RI + TA	P = 0.04 for RI vs RI + RO P = 0.03 for RI vs RI + TA NS for RI + RO vs RI + TA

RI: rizatriptan; RO: rofecoxib; TA: tolfenamic acid; n: number of attacks with nausea; N: number of treated attacks.

Nausea was present in 80 attacks (43.5%) at baseline (27 attacks of Group 1, in 28 attacks of Group 2 and in 25 attacks from Group 3). After 2 hours and 4 hours, less patients treated with RI + RO had nausea than those treated with the single use of RI (p = 0.017). At 4 hours, less patients treated with RI + TA had nausea than those treated with the single use of RI (p = 0.032). There were no statistically significant differences between the attacks treated with the combinations RI + RO and RI + TA in all time points (Table 3).

Photophobia was present in 102 (55.4%) of the 184 treated attacks at baseline. After 2 hours and 4 hours less patients treated with the RI + RO had photophobia than those treated with the single use of RI (respectively p =

0.010 and p = 0.023) or with the RI + TA (p = 0.003 and p = 0.015) (Table 4).

Recurrence was observed in 50% of the attacks treated with RI alone compared to 15,4% of those attacks treated with the combination of RI +RO, and 7.7% of those attacks treated with the combination of RI + TA. (Table 5, p < 0.01 for RI vs. RI + RO; p < 0.01 for RI vs. RI + TA; p=NS for RI + RO vs. RI + TA).

Adverse events were observed in 15 (25.8%) attacks treated with RI, 17 (27.4%) treated with RI + RO, and 21 (32.8%) attacks treated with RI + TA (NS for all comparisons). Adverse events were mild and transient. In the group treated with RI alone, the most frequent adverse events were somnolence (8.6% of the attacks) and dizzi-

Table 4: Absence of photophobia at consecutive timepoints.

Treatment	1 hour n/N (%)	2 hours n/N (%)	4 hour n/N (%)
RI	8/32 (25%)	15/32 (46.9%)	23/32 (71.9%)
RI + RO	15/34 (44.1%)	26/34 (76.5%)	32/34 (94.1%)
RI + TA	8/36 (22.2%)	17/36 (47.2%)	26/36 (72.2%)
P value	P = NS for RI vs RI + RO P = NS for RI vs RI + TA P = 0.02 for RI + RO vs RI + TA	P = 0.01 for RI vs RI + RO P = NS for RI vs RI + TA P = 0.003 for RI + RO vs RI + TA	P = 0.01 for RI vs RI + RO P = NS for RI vs RI + TA P = 0.01 for RI + RO vs RI + TA

RI: rizatriptan; RO: rofecoxib; TA: tolfenamic acid; n: number of attacks with photophobia; N: number of treated attacks.

Table 5: Recurrence rates according treatment group.

Treatment	Recurrence Rate n/N (%)
RI	11/22 (50%)
RI + RO	6/39 (15.4%)
RI + TA	2/26 (7.7%)
P value	P < 0.01 for RI vs RI + RO P < 0.01 for RI vs RI + TA P = NS for RI + RO vs RI + TA

RI: rizatriptan; RO: rofecoxib; TA: tolfenamic acid; n: attacks where recurrence were observed; N: number of treated attacks.

ness (8.6%). In the group treated with RI + RO, dyspepsia happened in 4.8% of the attacks. Chest pain and tachycardia were observed in one attack each. In the group treated with RI + TA, dyspepsia happened in 6.2% of the attacks.

Discussion

This prospective randomized study demonstrated that the combination of RI and a NSAID is associated with better efficacy, decrease of associated symptoms, and decrease on recurrence rates, compared to RI alone. However, our data must be analyzed with caution. First, this is an open study with inherent methodological flaws. Second, our sample size is small, which may explain recurrence rates of RI higher than usually presented in controlled studies. Third, we didn't assess patient's satisfaction with each of the chosen drug regimens. We tried to reduce the limitations by randomizing patients in counterbalanced order, thus reducing bias and increasing statistical power.

The triptans are a class of compounds acting through an agonistic action at 5-HT_{1B/1D} receptors. Incomplete relief in some patients, as well as recurrence of pain after complete relief, may counteract adherence by not addressing patient's expectations toward the acute migraine treatment [8,9,19]. In a previous study, we had already suggested that the combination of a triptan plus a NSAID improves efficacy in clinical practice not only due to the

decrease in the recurrence rates, but also due to better efficacy [13-15].

This study aimed to further investigate this hypothesis, by assessing the efficacy of a long-acting NSAID with proven efficacy in the acute treatment of migraine [20] combined with RI, as well as RI associated with a traditionally effective NSAID. TA was chosen due to its action in the leukotriene synthesis as well [21-23].

Our findings are supported by previous studies. A study assessing the efficacy of sumatriptan plus TA showed a reduction in the recurrence rate from 62,5% to 23,8%; with the combination of naproxen sodium plus sumatriptan, the recurrence rates were 59% and 25.5%. A study assessing the efficacy of RI + RO showed recurrence rates of 53% and 20% [13-15]. Interestingly, in our study the combination of RI +RO was significantly better not only compared to the use of RI alone but also compared to RI + TA with regard to pain free measures at 2 hours and photophobia at 1, 2 and 4 hours.

The figures obtained in the present study were different than those we observed in a previous trial comparing 10 mg RI with 10 mg RI + 25 mg RO [15]. In that study, respectively 42%, 76.5% and 87.6% of the attacks treated with the combination of RI + RO were pain free at 1, 2 and 4 hours. With regard to nausea, 49.1%, 79.2% and 90.6% of the attacks with nausea at baseline were nausea free at the time points 1, 2 and 4 hours. Although not significant, there was a trend for the superiority of the combination group over those taking RI alone, which was confirmed in the present trial.

Rofecoxib shows clinical efficacy in studies of patients with osteoarthritis and rheumatoid arthritis, similar to diclofenac, naproxen and ibuprofen, all proven effective in the acute treatment of migraine [10,24,25]. A recent controlled study demonstrated the superiority of RO 25 mg and RO 50 mg against placebo. Both doses were more effective in providing headache relief, as well as improving nausea and photophobia [20]. Its use in the short-

term prevention of peri-menstrual migraine has been also suggested in an open study [26]. In addition to its proven efficacy, RO is followed by a significant lower incidence of upper-gastrointestinal adverse events, such as perforations, ulcers and bleeds [24,25].

Tolfenamic acid is not only effective in migraine attacks but may have comparable efficacy, according to some studies, with ergotamine and sumatriptan. Studies show that TA may provide relief in up to 77% of the patients at 2 hours [21,27].

Conclusions

Drug combinations in migraine treatment are common among specialists and have a long background of fundamentals. Different neurotransmitter systems may be involved in migraine pathophysiology as well as different mechanisms may be involved in a migraine attack. Targeting it, when treating the patient, does represent a potential way of achieving better results. Attempts to increase efficacy and achieve patient's expectations can also represent the difference between being effective or keep the adherence in a patient's treatment [28-30]. Further controlled studies are warranted to confirm these observations.

Competing Interests

None declared.

Author's contributions

AVK carried out the patient's selection, inclusion, treatment, collecting the data and writing the initial manuscript.

MEB carried out the revision of the statistical analysis as well as the revision of the initial version of the manuscript.

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