RESEARCH ARTICLE

The first comparative double-blind trial on efficacy and safety of ergotamine based five-component combination and sumatriptan in migraine without aura

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Abstract

Background: Dihydroergotamine or ergotamine are the most effective preparations for aborting acute attacks of migraine without aura.

Objective: The aim of our study was to compare the efficacy and safety of ergotamine based five-component drug combination and sumatriptan in the treatment of moderate to severe acute attacks of migraine without aura.

Methods: The study was designed as a randomized, double-blind, double-dummy, placebo-controlled, parallel arm, multi-center clinical trial. The enrolled patients having migraine without aura were randomized to one of the study arms, ergotamine based five-component drug combination or sumatriptan.

Results: In total, 201 patients were randomized to one of the treatment arms. Higher percentage of patients was completely free of the headache two hours after dose administration in the ergotamine-based medication group compared to the sumatriptan group, regardless whether all (51.12 % vs 33.70 %) or only repeated attacks were taken into account (50.91 % vs 23.73 %); the salvage therapy (diclofenac) utilization rate was also lower in the ergotamine-based medication group (relative risk 0.61). Photophobia, phonophobia, and osmophobia were reversed more frequently in the ergotamine-based medication group (51.12 % vs 33.70 %), and failure to abort an attack of the migraine without aura occurred more frequently in the group treated with sumatriptan (1.1 % vs 4.9 %). The headache intensity two hours after ingestion of the study medication increased more frequently with sumatriptan, while other adverse events were rare in both groups.

Conclusions: This study demonstrated higher efficacy and similar safety of ergotamine based fixed drug combination in comparison to sumatriptan, when used in the treatment of an acute attack of the migraine. HIPPOKRATIA 2018, 22(1): 17-22.

Keywords: migraine without aura, sumatriptan, ergotamine based fixed drug combinations, efficacy, safety

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Introduction

The migraine without aura (MWA, earlier known as "a common migraine") is a type of a migraine manifested by recurrent attacks of prolonged, severe, pulsating headache (4 to 72 hours), and accompanied with neurological (phonophobia and photophobia) and gastrointestinal (nausea) symptoms. The attacks occur without previous warning signs[1]. A migraine, in general, is disabling condition[2] with high lifetime prevalence in the USA (affects one out of seven subjects) and Europe (14.7 % of adults[3]), and more than half of the cases could be classified to type without aura (lifetime prevalence about 8 % in Denmark, 11 % in Ukraine, 11 % in Croatia). It is characterized by a low quality of life and high indirect costs due to absenteeism and productivity loss; among neurological disorders, the migraine follows only dementia regarding the total burden for the society[3-5].

Treatment of the acute attacks of migraine is administered with intent to reverse or cease the progression of the headache. Although many medications have been used previously for that purpose, attacks of MWA are nowadays best aborted by dihydroergotamine or ergotamine[5].

Although all of these medications act through serotonergic receptors, derivatives of ergot alkaloids also activate a lot of other mechanisms which contribute to the overall effect (alpha-adrenergic stimulation, activation of dopamine D2 receptors, etc.). Combining ergotamine with analgesics and other vasoactive drugs may bring additional therapeutic benefits and increase the efficiency of aborting an attack of a migraine, as already shown for the combination of ergotamine and caffeine[6,7]. Ergotamine-based combination was approved a long time ago as a combination of propyphenazone (analgesic), caffeine, camylofin chloride (anticholinergic and direct vasodilator), mecloxamine citrate (anticholinergic, antihistaminic, mild sedative and antiemetic) and ergotamine tartrate, and its efficacy and safety in treating attacks of a migraine were demonstrated in previous clinical studies[6].

Although triptans are nowadays considered as the first-line drugs for aborting attacks of the MWA, their efficacy and safety have never been compared to complex fixed drug combinations against a migraine, such as ergotamine-based combination[7]. They had been compared to a combination of ergotamine and caffeine only[7,8]. The aim of the current study was to compare the efficacy and safety of the ergotamine-based combination and sumatriptan in the treatment of moderate to severe acute attacks of migraine without aura.

Patients and Methods

The study was designed as a randomized, double-blind, double-dummy, placebo-controlled, parallel arm, multi-center clinical trial. It was conducted according to the ICH E6 (R1) Guideline for Good Clinical Practice and the latest revision of Helsinki declaration (2013) at five study sites in Bosnia and Herzegovina: the University Clinical Centre (UCC) of Republika Srpska in Banja Luka, UCC Tuzla, UCC Sarajevo, Clinical Hospital of Mostar, and the Cantonal Hospital "Dr. Safet Mujić" of Mostar. Prior to commencement, the study was approved by the Agency for Medicinal Products and Medicinal Devices of Bosnia and Herzegovina (No 08-07.5-3269-1/15, date: 01/07/15) as well as by the independent local Ethical Committees of the Clinical Centre University of Sarajevo (dated 28/05/15), University Hospital Clinical Centre of Banja Luka (No 01-9-144.2/15, date: 29/04/15), University Clinical Centre of Tuzla (No 02-09/2-41/15, date: 27/05/15), Cantonal Hospital "Dr. Safet Mujić" of Mostar (No 01-1-2445/15, date: 12/05/15) and University Clinical Hospital Mostar (No 3448/15, date: 27/05/15). The study was conducted from the 1st July 2015 to the 31st October 2017, and the enrolment of the patients took place from the 1st September 2015 to the 1st August 2017.

The inclusion criteria were as follows: patients of both sex, 18 to 64 years old, with a diagnosis of MWA, onset of migraine before the age of 50, duration of the disease for at least two years (according to the International Headache Society diagnostic criteria), one to six attacks per month during the 6-month-period before the screening, outpatients, sustained dosing regimen of prophylactic medication (if any) for at least two months, moderate or severe headache on a 4-level scale (0: without pain, 1: mild pain, 2: moderate pain, 3: severe pain) recommended by the Guidelines for controlled trials of drugs in migraine[9], normal cognition and ability to read, understand and complete the Patient Diary by their own. The exclusion criteria were: worsening of the migraine, the intention of female patients to get pregnant or pregnancy during the trial, severe adverse drug events, co-morbidities, hospitalization during the trial and non-adherence to the study protocol. The patients were enrolled after the screening and signing the informed consent form.

The enrolled patients were randomized to one of the study arms in blocks of four, by a statistician blinded for the patient details. Random number generator from Microsoft Excel was used to assign the study medication pack codes (each containing one of the study drugs) to the patient codes, and the information was communicated to the investigators by phone. The investigators were blinded for the contents of the study medication packs, an explanation of the medication code assigned to a patient was supplied in a sealed envelope, and the investigator was not allowed to open the envelope except in the case of emergency. The prophylactic medication was discontinued immediately after the randomization and the following 14 days were reserved for a washout period. Each of the study participants received two drug packages (bottles), both with two tablets inside; the patients randomized to the ergotamine-based combination group received in each package one tablet of the ergotamine-based combination and another tablet of placebo with the same appearance as the sumatriptan tablet, while the patients randomized to sumatriptan group received in each package one tablet of sumatriptan and another tablet of placebo with the same appearance as the ergotamine-based combination. The medications and dummies were provided by the Research & Development Unit of Bosnalijek, Sarajevo. The patients were instructed to swallow both tablets from the first bottle immediately after the onset of a headache, and two hours later to take both tablets from the second bottle if the headache did not wear off completely after the first dose. If the headache was still present two hours after the second dose, the patients from both groups were allowed to take diclofenac 50 mg orally (they were supplied with one blister containing ten coated tablets of diclofenac potassium). The patients were monitored for one month. If the patients experienced repeated attacks, they were administered the same medication as in the first attack of the MWA.

The primary outcome of the study was the rate of complete disappearance of the headache two hours after taking the study medication. Secondary outcomes investigated were: a decrease in headache intensity after taking the study medication, reversal of photophobia, phonophobia, and osmophobia, the intensity of the headache at defined time points after the study medication, as measured by visual analogue scale, an increase of headache intensity two hours after taking the study medica-

tion, tolerance of the study medication and frequency of any drug-related adverse events. The effects of the study medication on headache and accompanying phenomena were estimated by both study investigators and the patients themselves. The estimate of tolerability and safety of the study medication was based on monitoring of any adverse events.

Statistical analysis

The sample size calculation was based on the effect size observed in previous studies (20 % difference in response rate of moderate to severe attacks to the study medication[10]), using two-sided Chi-square test, the probability of the first-type statistical error of 0.05 (α =0.05), and expected 80 % power of the study (β =0.20). The data were at first described by measures of central tendency (mean and median) and dispersion (standard deviation and range). Values of the continuous variables in the study groups were compared by the Student's t-test if the normal distribution of the data was confirmed, and by the Mann-Whitney test, if else. Frequencies and proportions in the study groups were compared by Chi-square test. The null hypothesis was considered correct if its probability was equal or less than 0.05. All calculations were made by the MedCalc software, version 11.6.1.0 (MedCalc Software, Ostend, Belgium).

Results

Two hundred and one patients were randomized to one of the treatment arms (group A: ergotamine-based medication group; group B: sumatriptan group), 168 females (82 in group A and 86 in group B) and 33 males (16 in group A and 17 in group B). Thirteen patients (five from group A and eight from group B) were excluded from the study as they either did not have at least three acute attacks of MWA during the follow-up, or their attacks were of mild intensity. A total of 188 patients completed the study (93 in group A, and 95 in group B). The average patients' age was 41.2 years for group A and 40.9 years for group B. The patient characteristics at the baseline are shown in Table 1.

The effects of the study medication on the primary and secondary outcomes are shown in Table 2. The decrease in headache intensity (as measured by the visual analogue scale) during the eight hours following the administration of the first dose of the study medication is shown in Figure 1. The consistency of the benefit observed after the first attack was noted in 46.3 % of the patients (n =41) with repeated attacks who were administered ergotamine-based medication, and in 25.6 % of the patients (n =43) with repeated attacks who were administered sumatriptan (chi-square: 3.893, p: 0.0485). The MWA attacks in females responded more frequently (chi-square: 9.787, p: 0.0018) to ergotamine-based drug (78/154, 50.7 %) than to sumatriptan (52/157, 33.1 %). The similar direction of difference was observed with the MWA attacks in males, which responded more frequently to the ergotamine-based drug (13/24, 54.2 %) than to sumatriptan (10/27, 37.0 %); however, the difference was not significant (chi-square: 1.476, p: 0.2244).

Only one adverse drug event was reported in the trial, and it was not serious (one female patient complained of feeling "fullness in the head" after taking ergotamine-based medication). One female patient in the ergotamine-based medication arm became pregnant during the study, and was therefore excluded; the follow-up revealed that pregnancy and birth were uneventful. At the end of the study, the patients were questioned whether they would use the same study medication again, and 66 (71 %) responded positive in the ergotamine-based medication arm, while 66 (69.5 %) in the sumatriptan arm. None of the patients in either of the study groups reported intolerance to the study medication.

Discussion

In our study, ergotamine-based medication demonstrated superior efficacy over sumatriptan in patients with attacks of MWA. More patients were completely free of the headache two hours following the intake of dose in the ergotamine-based medication group (group A) compared to the sumatriptan group (group B), regardless whether all or only repeated attacks were taken into account; the rate of use of salvage therapy (diclofenac) was also lower in the ergotamine-based medication group (relative risk 0.61). While the decrease in the headache intensity over eight hours after taking the study medica-

Table 1: Baseline characteristics of the 201 patients with migraine without aura who were enrolled in the study and randomized into the ergotamine-based medication group or the sumatriptan group.

Variable	group A n: 98	group B n: 103	test used, significance
Age (years): mean ± SD	41.16 ± 11.78	40.90 ± 9.78	t-test (186): -0.136, p: 0.8923
Sex: female/male (%)	82/16 (84 %/16 %)	86/17 (84 %/16 %)	chi-square: 0.003, p: 0.9500
Duration (years) of MWA before screening median (95 % CI)	8.00 (6.00-10.00)	10.00 (8.00-10.00)	Mann-Whitney U: 3612.50, z: 1.373, p: 0.1697
Number of attacks per month during the 6-month period before screening: mean ± SD	2.082 (±2.3393) median 1.000 (1-20)	1.830 (±1.4074) median 1.000 (1-8)	Mann-Whitney U: 4566.00, z: 0.793, p: 0.4275
Percent of patients receiving prophylactic medication before screening	0	0	Not applicable

MWA: migraine without aura, group A: ergotamine-based medication group, group B: sumatriptan group, n: number, SD: standard deviation, CI: confidence intervals.

Table 2: Outcomes of the study which compared the efficacy and safety of ergotamine based five-component drug combination and sumatriptan in the treatment of moderate to severe acute attacks of migraine without aura.

Outcome	group A n: 93	group B n: 95	test used, significance
Rate of complete disappearance of headache two hours after intake of the study medication (all attacks)	51.12 % (91 of 178 attacks)	33.70 % (62 of 184 attacks)	chi-square: 10.024, p: 0.0015
Rate of complete disappearance of headache two hours after intake of the study medication (repeated attacks)	50.91 % (28 of 55 attacks)	23.73 % (14 of 59 attacks)	chi-square: 7.779, p: 0.0053
Rate of complete disappearance of headache two hours after intake of the first film tablet of the study medication (all attacks)	26.97 % (48 of 178 attacks)	21.74 % (40 of 184 attacks)	chi-square: 1.341, p = 0.2468
Rate of complete disappearance of headache two hours after intake of the second film tablet of the study medication (all attacks)	24.16 % (43 of 178 attacks)	11.96 % (22 of 184 attacks)	chi-square: 9.115, p: 0.0025
Rate of use of salvage therapy (diclofenac)	21.35 % (38 of 178 attacks)	34.78 % (64 of 184 attacks)	chi-square: 8.095, p: 0.0044
Decrease in headache intensity after ingestion of the study medication	31.36 ± 26.31 95 % CI: 26.78-36.93	26.36 ± 27.47 95 % CI: 21.33-31.39	Difference: -4.99 t-test (203): -1.312, p: 0.1910
Average severity of pain intensity during migraine attacks	74.946 ± 14.036	71.684 ± 17.844	Mann-Whitney U: 15740.50, z: 1.177, p: 0.2390
Reversal of photophobia, phonophobia, and osmophobia	51.12 % (91)	33.70 % (62)	Chi-square: 10.024, p: 0.0015
Failure of therapy to abort an attack of migraine without aura	1.1 % (2 of 178)	4.9 % (9 of 184)	chi-square: 11.748, p: 0.0006
Frequency of drug related adverse events	0.6 % (1 of 178)	0 %	Not applicable
Increase of headache intensity two hours after ingestion of the study medication	0 % (0 of 116)	5.98 % (7 of 117)	chi-square: 5.422, p: 0.0199

Group A: ergotamine-based medication group, group B: sumatriptan group, n: number, CI: confidence intervals.

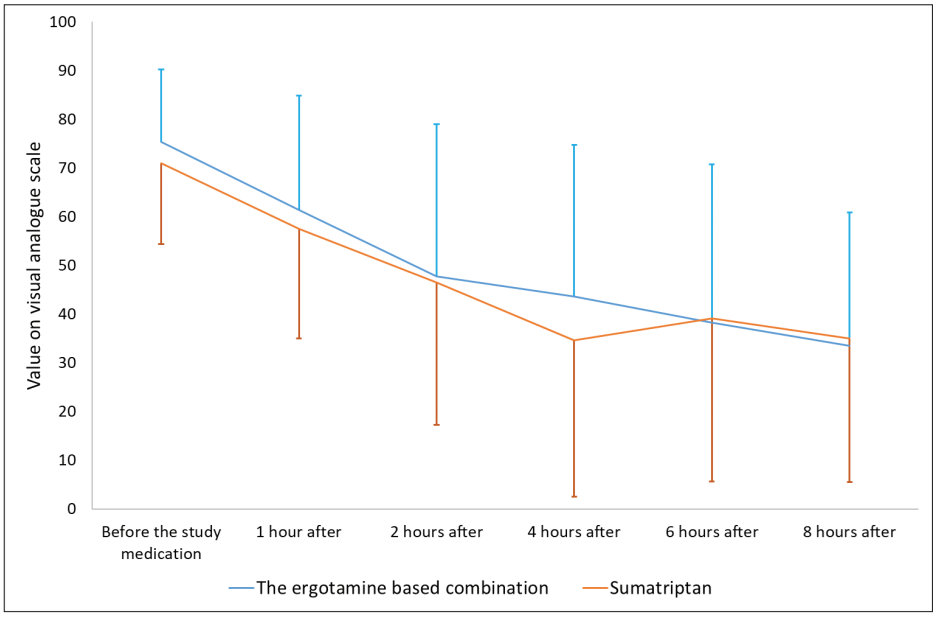

Figure 1: Intensity of headache (as measured by the visual analogue scale from 0 to 100) during the eight hours after administration of the first dose of study medication.

tion demonstrated similar rates in both groups, photophobia, phonophobia, and osmophobia were reversed more frequently in patients of group A, and failure of aborting an attack of MWA occurred more often in patients of group B. Increase in headache intensity two hours after intake of the study medication was more frequent with sumatriptan, while other adverse events were rare in both groups.

The ideal innovative medication for treating acute attacks of migraine should be more efficient, with a lower number of adverse effects, less interacting with other drugs and less costly than standard therapy[11]. It is an important issue for patients suffering from migraine, as this is a debilitating disorder which affects mostly young and employed people; the quality of life is significantly decreased, and costs for both health insurance funds and society as a whole are enormous and constantly increasing[12-16]. Both ergotamine and triptans (sumatriptan, zolmitriptan, naratriptan, etc.) are considered as specific drugs for the abortion of acute attacks of migraine[3] with a clearly defined mechanism of action. Efficacy and safety of triptans when used for therapy of migraine were compared in several trials with the combination of ergotamine and caffeine. Almotriptan, rizatriptan, and sumatriptan were compared with the combination of ergotamine and caffeine in clinical trials: efficacy of triptans was higher in all trials, but the difference was not significant enough to preclude further usage of ergotamine in clinical practice[17-19]. Interestingly, the safety of triptans and that of ergotamine/caffeine combination were not significantly different - the medications were tolerated well, and overall frequency of adverse events was low. However, no clinical trials ever compared a fixed combination of ergotamine/caffeine alone or with other adjuvant drugs versus triptans for the abortion of attacks of migraine.

Indeed, triptans were more effective than ergotamine in certain aspects when used for attacks of a migraine, but their serious drawbacks were the high price and short duration of action[20]. Abortion of the attacks and the disappearance of pain were more frequent with sumatriptan, but ergotamine decreased the number of relapses, and its effect was overall better when the whole 24-hour period of action was accounted. Ergotamine based combinations are exceptionally efficient for the treatment of very long attacks of migraine and in patients with multiple relapses of the attacks[21]. The long duration of action favors ergotamine-based combinations for the treatment of women suffering from a menstrual migraine, whose attacks may last for several days[22]. Ergotamine based combinations are also recommended for patients with a migraine who abuse analgesics or triptans, in order to mitigate or abort attacks during abstinence of drugs which caused an iatrogenic headache. Nausea and vomiting are the least tolerable symptoms during attacks of migraine for some patients. Dihydro-derivative of ergotamine, dihydroergotamine, causes nausea and vomiting less frequently than ergotamine[23].

Apart from ergotamine and caffeine, the ergotamine-based study medication also contained analgesic propyphenazone and anticholinergics camylofin and mecloxamine, which contributed to the overall efficacy of the drug. A combination of drugs against migraine such as this one has not been previously tested in clinical trials, but there are several published case series showing its efficacy in patients having an attack of a migraine[24,25]. Our study demonstrated for the first time superior efficacy of the fixed combination of five compounds over triptans for aborting attacks of migraine without aura, a result which suggests synergistic action of the compounds that have different molecular mechanisms of action. This beneficial effect was not achieved at the expense of safety, as adverse events were infrequent and not severe. However, although statistically significant, the differences in the efficacy of ergotamine-based combination and sumatriptan are not that clinically important, and both types of drugs could be successfully used in practice to abort attacks of the MWA.

The relatively low sample size and the single testing of the study medication in a significant proportion of the study patients were the main limitations of the current study. The disappearance of pain was based on the patients' subjective estimate, which is the usual methodological problem for the majority of clinical trials on migraine.

In conclusion, our study demonstrated a higher efficacy, according to a variety of outcomes, of ergotamine-based, five-component drug combination compared to sumatriptan when used for the treatment of an acute attack of MWA. The patients taking the ergotamine-based medication less frequently used salvage therapy for treating headache than the patients taking sumatriptan, and both medicines were essentially without adverse effects.

Conflict of interest

The authors declare no conflict of interest in regard to contents of this article.

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