PharmacologyOnLine

Archives • 2021 • vol.2 • 882-889

TRIMODALITY APPROACH TO MIGRAINE PHARMACOTHERAPY: THE IMAGE STUDY

Ivanov, D. D.[1]; Gozhenko, A. I.[2]; Ivanova, M. D.[1]; Badiuk, N.[3]*

[1]PL Shupyk National University of Healthcare of Ukraine, Kyiv, Ukraine

[2]State Enterprise Ukrainian Research Institute of Transport Medicine of the "Ministry of Health of Ukraine", Odesa

[3]International European University, Kyiv, Ukraine

*badiuk_ns@ukr.net

Abstract

The article presented is devoted to the analysis of a possible new approach to the treatment of migraine attacks. To date, there are several medical practices for their treatment. Their efficiency is on average from 30 to 80%. However, the presence of numerous approaches to therapy, including non-drug, indicates a complex mechanism of migraine pain.

The objective: to test the idea of polypill (a co-formulated pill) use for relieving migraine pain.

Materials and methods. A three-component combination that affects the various links in the formation of migraine pain has been proposed, namely: the nonsteroidal anti-inflammatory drug *nimesulide* at a dose of 100 mg, the selective 5HT1B / 1D receptor agonist *zolmitriptan* 2.5 mg and the selective beta-blocker *nebivolol* 5 mg became part of one remedy in certain therapeutic concentrations. 21 persons with more than 3 years of migraine attacks history participated at the research. POEM was a study design, 6-month pilot open single-center prospective controlled randomized in one group with historical control. Evaluation of the effectiveness of pain relief was performed on the MIDAS scale.

Results and discussion. 21 participants were randomized, 20 people completed the study. The efficacy of the triple combination on the MIDAS score significantly reduced the severity of migraine attacks (P≤0.05), which was accompanied by a decrease in the relative risk of severe disability (RR 1,667, 95% CI from 0.619 to 4,486, NNT 7.5) compared with mild disability (RR 1,575, 95 % SI from 0.685 to 3.619, NNT 6.08). The effectiveness of reducing the MIDAS score by 25% or more when using triple therapy was higher in females RR 1.667 (95% SI from 0.666 to 4.171, NNT 3.5) and among women over 40 y. o. RR 2,333 (95% SI from 0.373 to 14.614, NNT 2.75). In general, the triple combination showed higher efficacy in complete pain relief within 2 hours after treatment: 90% vs. 66% (P≤0.1): RR 1,350 (95% CI from 0.965 to 1.889, NNT 4.29). The possibility of creating a combined drug in one tablet is discussed.

Conclusions. The use of a triple combination of drugs in a migraine attack resulted in a statistically significant compared to standard subject therapy for migraine pain relief within two hours of administration, a reduction in the three-month MIDAS score, and facilitated the transition from Level 3 of disability according to MIDAS grade to a lower level. in the patients under observation. The triple combination was well tolerated and was most effective in women over 40 years of age. Further studies are needed to obtain clinical recommendations for the use of the tested combination.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

Keywords: *migraine treatment, polypill – drugs triple combination, nimesulide, zolmitriptan, nebivolol*

Introduction

Migraine is one of the headache varieties which often causes disability. Its attack can cause severe throbbing pain, usually on one side of the head, which is often accompanied by nausea, vomiting and extreme sensitivity to light, sound or smell [1]. Migraine attacks can last from hours to days, and the pain can be so severe that it interferes with work, social and daily activities. Approximately two thirds of migraine cases are familial in nature with a twofold predominance in females [2]. The prevalence among adults is quite high, for example, in the United States migraine affects approximately 1 in 6 Americans and 1 in 5 women over a 3-month period [3].

Migraine can occur in four stages: prodrome, aura, attack and post-drome. Not everyone who suffers from migraines goes through all the stages, which can be interrupted by adequate drug therapy. To date, 5 groups of drugs show the greatest effectiveness in the treatment of migraine attacks: 1) non-selective and selective agonists of serotonin receptors, in particular agonists of 5HT1B / 1D receptors – triptans; 2) nonsteroidal anti-inflammatory drugs; 3) beta-blockers; 4) antidepressants, in particular amitriptyline and venlafaxine and 5) anti-calcitonin gene-related peptides, including eptinezumab, erenumab, fremanezumab and galcanezumab [4]. None of these groups is absolutely decisive in the treatment of seizures in general or in a particular person, because the mechanism of the attack is much caused and differs even in specific situations in the same subject.

The working hypothesis of the study was to increase the effectiveness of migraine attacks treatment due to the simultaneous effect of different drugs on the unrelated mechanisms of migraine development [5].

The objective: to test the idea of polypill (a three component co-formulated pill) use for relieving migraine pain.

Methods

The essence of the approach proposed is the simultaneous use of a combination of three drugs of different action in the doses prescribed by official instructions, namely: *nimesulide* at a dose of 100 mg, selective agonist 5HT1B / 1D-receptors *zolmitriptan* 2.5 mg and selective beta-blocker - *nebivolol* 5 mg, which became the essence of severe migraine attacks treatment - IMAGE trial.

The conducted IMAGE study belongs to the second class of clinical trials, namely: POEM (Patient-Oriented Evidence that Matters) [6], 6-month pilot open one-center prospective controlled randomized in one group with historical control. All the study participants gave informed consent to participate in it.

21 participants were randomized and observed for 3 months against the background of their usual seizure therapy, and then they were prescribed three-component therapy in the presence of migraine attacks. Thus, they themselves formed a control group during the first three months of observation (Fig. 1).

Evaluation of the effectiveness of pain relief was performed on the MIDAS scale [7]. Statistical analysis of absolute values, percentages and 50% of the interquartile range was performed to assess significant differences ($P \leq 0.05$) and calculate the absolute and relative risks of events [8, 9].

Results

21 participants with a history of migraine suffering over 3 years (5 ± 0.6) were included in a prospective IMAGE pilot study, of which 20 subjects completed the study (one person dropped out at 5 months of follow-up). Characteristics of the study participants are shown in Table 1.

According to the Table 1 data, the groups that started and completed the study were completely homogeneous without statistical differences. The use of the triple combination did not reduce the number of migraine attacks.

20 persons have completed the study. Among them 18 persons (90%) received a triple drug combination during migraine attacks at the following doses: *nimesulide* of 100 mg / *zolmitriptan* 2.5 mg / *nebivolol* 5 mg. Two women aged 21 and 25 y. o. received *nimesulide* 100 mg / *zolmitriptan* 2.5 mg / *nebivolol* 2.5 mg due to natural hypotension (100-105 / 60-65 mm Hg).

Table 2 shows the results of the effectiveness of the triple combination in comparison with the three-month control on standard therapy on the MIDAS scale.

As follows from Table 2, the appointment of a triple combination significantly reduced MIDAS score (P≤0.05), which was accompanied by a decrease in the relative risk of severe disability (RR 1,667, 95% CI from 0,619 to 4,486, NNT 7.5) compared with mild disability (RR 1,575, 95% SI from 0.685 to 3.619, NNT 6.08).

The effectiveness of reducing the MIDAS score by 25% or more when using triple therapy was higher in females RR 1,667 (95% CI from 0.666 to 4,171, NNT 3.5) and among women over 40 y. o. RR 2,333 (95% CI from 0.373 to 14,614 , NNT 2.75).

In general, the triple combination showed higher efficacy in complete pain relief within 2 hours after treatment: 90% vs. 66% before its administration (P≤0.1): RR 1,350 (95% SI from 0.965 to 1.889, NNT 4.29).

Patient tolerability of the triple combination, which was defined as the patient's non- refusal to re-prescribe it, was 95%, unwillingness to continue to take the triple combination was demonstrated by one person (5%) who dropped out of the study.

Discussion

Treatment of migraine attacks in adults and children is an urgent problem [10, 11]. It has long been known about the effectiveness of non-steroidal anti-inflammatory drugs in the treatment of mild to moderate migraine attacks [12, 13]. One of the most effective NSAIDs for the treatment and prevention of migraine is nimesulide. If seizures cannot be stopped with non-steroidal anti-inflammatory drugs, drugs with more pronounced specific action (triptans) are prescribed [14]. 5-HT1B / 1D receptor agonists - *sumatriptan, zalistriptan, naratriptan, almotriptan* - are drugs for the treatment of migraine and should not be used in other types of headache, except for cluster headaches.

In the presence of hypertension during the attack – fast - acting antihypertensive drugs, such as *captopril* or beta-blocker show definite effectiveness [15]. Beta-blockers have been used to treat migraines for more than 25 years and are considered one of the most effective drugs [16]. The antihypertensive effect of renin-angiotensin system inhibitors also demonstrates some potential in the treatment of migraine attacks [17].

Antidepressants, in particular *amitriptyline* and *venlafaxine,* have been offered for many years to treat migraine attacks [18]. Medications for the treatment of epilepsy also show some positive results in the treatment of migraine attacks [19].

In recent years, active testing of anti-calcitonin gene-related peptides, including *eptinezumab, erenumab, fremanezumab and galcanezumab* [20] is being conducted. They have a more targeted impact, but are much more expensive [21].

The presence of a large number of therapeutic approaches, of which we have considered only a part, indicates the lack of a highly effective means to stop the attack of migraine. When prescribing drugs to relieve migraine attack one should take into account the severity and frequency of attacks, the presence of other symptoms, the wishes of the person and the history of treatment. It is possible that the solution lies in the simultaneous impact on various parts of the process, as proposed in the presented IMAGE pilot study.

The IMAGE results obtained show that the simultaneous effect on many links in the development of migraine attack is more effective than conventional therapy. Observations have shown that the rate of seizure relief increases, the power of the effect is greater, the tolerability of the combination is good. Better efficacy in women over the age of 40 indicates a possible increase in the hypertensive component of the attack. However, the correlation with baseline blood pressure, as well as some other issues, namely sample increase, side effect monitoring, individual dose selection, and others, need to be continued.

Conclusions

1. The use of a triple combination in migraine attack resulted in a statistically significant two-hour pain relief compared to standard subject therapy, a reduction in the three-month MIDAS score, and facilitated the transition from Level 3 of disability according to MIDAS grade to a lower level in the patients under study.

2. The triple combination to relieve migraine attack at a dose of *nimesulide* 100 mg / *zolmitriptan* 2.5 mg / *nebivolol* 5 mg may be considered for most subjects. In the presence of natural hypotension, a dose of *nimesulide* 100 mg / *zolmitriptan* 2.5 mg / *nebivolol* 2.5 mg is appropriate.

3. The triple combination is more effective in females and at the age over 40 y.o.

4. The triple combination showed higher efficacy and no increase in adverse reactions compared to previously known human therapy.

5. The use of a triple combination did not reduce the number of migraine attacks.

Acknowledgments

The authors declare that there are no conflicts of interest.

Funding: "Medical practice of prof. D. Ivanov ™

References

1. https://www.mayoclinic.org/diseases-conditions/migraine-headache/symptoms-causes/syc-20360201
2. Headaches in over 12s: diagnosis and management https://www.nice.org.uk/guidance/cg150/chapter/Recommendations#management-2
3. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies Headache. 2018 Apr;58(4):496-505. doi: 10.1111/head.13281. Epub 2018 Mar 12. PMID: 29527677
4. AAN Summary of Evidence-based Guideline for CLINICIANS Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults https://www.aan.com/Guidelines/home/GetGuidelineContent/545
5. Ivanov DD Modern approaches to migraine pharmacotherapy. Application Ukrpatent m 2021 02012 dated 02.02.2021

https://wilkes.libguides.com/c.php?g=191942&p=1266516

6. Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J Reliability of the migraine disability assessment score in a population-based sample of headache sufferers Cephalalgia. 1999 Mar;19(2):107-14; discussion 74. doi: 10.1046/j.1468-2982.1999.019002107.x. PMID: 10214536 DOI: 10.1046/j.1468-2982.1999.019002107.x

https://www.statisticshowto.com/calculators/interquartile-range-calculator/

https://www.gigacalculator.com/calculators/hazard-ratio-calculator.php

7. Gobel H. "1. Migraine". ICHD-3 The International Classification of Headache Disorders 3rd edition. Retrieved 22 October 2020.
8. Locher C, Kossowsky J, Koechlin H, Lam TL, Barthel J, Berde CB, et al. (April 2020). "Efficacy, Safety, and Acceptability of Pharmacologic Treatments for Pediatric Migraine Prophylaxis: A Systematic Review and Network Meta-analysis". JAMA Pediatrics. 174 (4): 341–349. doi:10.1001/jamapediatrics.2019.5856. PMC 7042942. PMID 32040139.
9. HavankaKanniainen H. Treatment of acute migraine attack: ibuprofen and placebo compared // Headache. – 1989. – Vol. 29. – P. 507–509.
10. Dahlof C., Bjorkman R. Diclofenac¬K (50 and 100 mg) and placebo in the acute treatment of migraine // Cephalalgia. – 1993. – Vol. 13. – P. 117–123.
11. May A, Burstein R (November 2019). "Hypothalamic regulation of headache and migraine". Cephalalgia. 39 (13): 1710–1719. doi:10.1177/0333102419867280. PMC 7164212. PMID 31466456.
12. Loder E, Burch R, Rizzoli P (June 2012). "The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines". Headache. 52 (6): 930–45. doi:10.1111/j.1526-4610.2012.02185.x. PMID 22671714. S2CID 540800.
13. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E (April 2012). "Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society". Neurology. 78 (17): 1337–45. doi:10.1212/WNL.0b013e3182535d20. PMC 3335452. PMID 22529202.
14. Dorosch T, Ganzer CA, Lin M, Seifan A (September 2019). "Efficacy of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in the Preventative Treatment of Episodic Migraine in Adults". Current Pain and Headache Reports. 23 (11): 85. doi:10.1007/s11916-019-0823-8. PMID 31515634. S2CID 202557362.

15. Pringsheim T, Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, et al. (March 2012). "Canadian Headache Society guideline for migraine prophylaxis". The Canadian Journal of Neurological Sciences. 39 (2 Suppl 2): S1-59. PMID 22683887.
16. Linde M, Mulleners WM, Chronicle EP, McCrory DC (June 2013). "Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults". The Cochrane Database of Systematic Reviews. 2021 (6): CD010608. doi:10.1002/14651858.CD010608. PMC 8221229. PMID 23797674.
17. Ibekwe, A.; Perras, C.; Mierzwinski-Urban, M. (2016). "Monoclonal Antibodies to Prevent Migraine Headaches". PMID 30855775.
18. Loder E, Renthal W (March 2019). "Calcitonin Gene-Related Peptide Monoclonal Antibody Treatments for Migraine". JAMA Internal Medicine. 179 (3): 421–422. doi:10.1001/jamainternmed.2018.7536. PMID 30640381. S2CID 58601441.

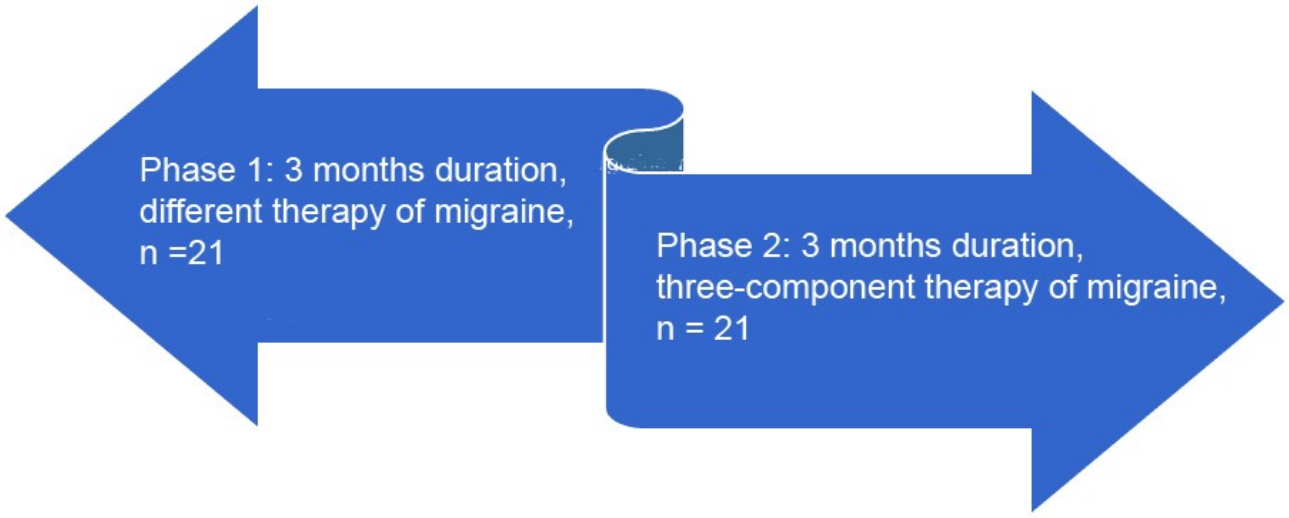

Figure 1. Research design

Table 1. Clinical characteristics of IMAGE study participants

Indicator / group	Number of subjects included in the study before the use of polypill treatment, n = 21 Stage 1: the first 3 months	The number of subjects who completed treatment, n = 20 Stage 2: the next 3 months
Women	14(67%)	14(70%)
Men	7(33%)	6(30%)
Women, age (years)	44.5(12)	33(12)
Men, age (years)	39(25)	40.5(19)
Age (years)	42(21.5)	43(16)
N of attacks, women	3(2)	3(2)
N of attacks, men	3(1)	2.5(1)
N of attacks	3(1.5)	3(1.5)
Pain relief within two hours of treatment administration	14(66%)	18(90%)

Note: data are presented in absolute values, %, 50 percentiles with indication in parentheses of the interquartile range

Table 2. Evaluation of the effectiveness of the triple combination on the MIDAS scale

	The number of subjects included in the study before the use of polyps treatment, n = 21 Stage 1: the first 3 months	The number of subjects who completed treatment, n = 20 Stage 2: next 3 months	Statistical significance of differences	Absolute risk (EER) / Relative risk (RR) on standard and triple therapy
MIDAS Score	24 ± 4	13 ± 3	p = 0.033960	
MIDAS Grade II	6 (29%)	9 (45%)	t = 0.643	0.450 / 1.575
MIDAS Grade III	6 (29%)	6 (30%)	t = 0.037	0.286 / 0.952
MIDAS Grade IV	7 (32%)	5 (25%)	t = 0.267	0.333 / 1.667

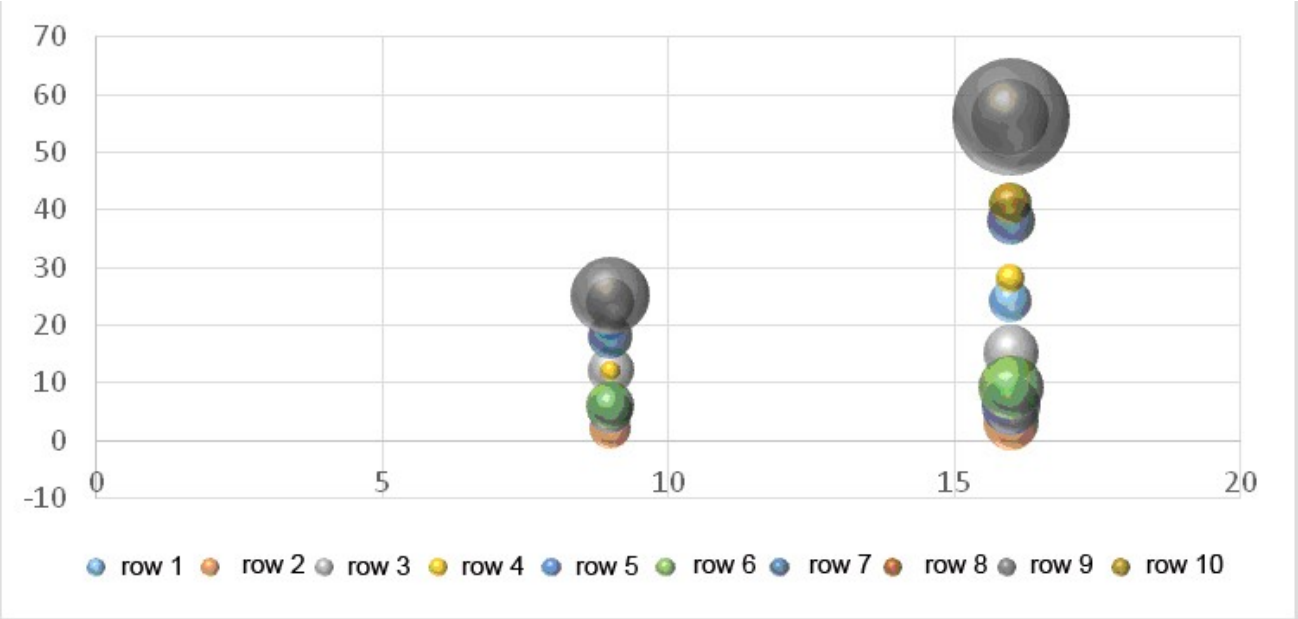

Figure 2. MIDAS score on standard therapy (right) and triple therapy (left)

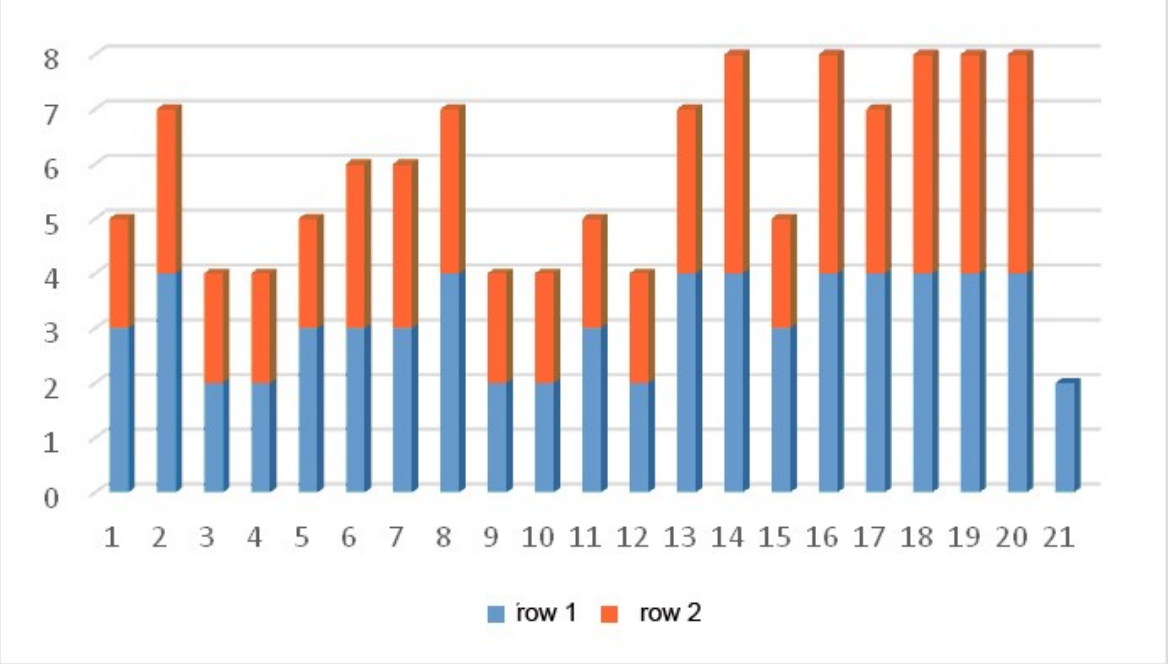

Figure 3. Level of disability according to MIDAS grade
Note: blue - triple therapy, orange - standard therapy