

**Chun Liu,
O.V. Pohorielov**

CLINICAL CHARACTERISTICS OF CEPHALALGIA AT PATIENTS WITH ARTERIAL HYPERTENSION DURING INTERMITTENT FASTING

SE «Dnipropetrovsk medical academy of Health Ministry of Ukraine»

Department of neurology and ophthalmology

V. Vernadsky str., 9, Dnipro, 49044, Ukraine

ДЗ «Дніпропетровська медична академія МОЗ України»

кафедри неврології і офтальмології

(зав. – д. мед. н. О.В. Погорєлов)

вул. В. Вернадського, 9, Дніпро, 49044, Україна

e-mail: aleksei.pogorelov@gmail.com.

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Abstract. **Clinical characteristics of cephalalgia at patients with arterial hypertension during intermittent fasting.** **Chun Liu, Pohorielov O.V.** *The study of the effectiveness and safety of intermittent fasting (IF) at 185 patients aged from 25 to 75 years (mean age – 48,6 years) with arterial hypertension (AH) and headache was carried out. AH was seen as the most likely factor of cerebral discirculation and associated cephalgia. Patients volunteered to maintain a short-term dietary restriction with terms of 16 or 24 hours once in 7 days over a period of 4 weeks. During this period, 43 patients stopped participation in the study, of which 31 - at 24-hour IF and 12 - at 16-hour IF. The assessment of the influence on cephalgia was considered positive when the score of visual analog scale (VAS) was decreased by 2 or more points and / or there was a significant decrease in the duration and frequency of cephalgia attacks. In a rhythmic diet with a 16-hour food intake missing, a positive result was registered at 35% (37,25% of young patients, 40,48% – of average and 28,57% of the elderly) without a significant difference between ages. The effectiveness of a 24-hour type of IF was higher and made up about 75% in all age groups. Negative side effects of IF that would require its termination due to objective reasons (threatening changes in blood pressure, syncope states and others) were not recorded, the most common complaints were the feeling of hunger (from 50 to 76% with a difference in age), psychological tension, uncertain anxiety (on average about 32%). The authors consider that such a psychological feature - namely, the impossibility and unwillingness to endure short-term fasting was a main factor of refusal to continue the treatment regimen, and within certain limits prevents the wider use of IF method in the treatment of cephalgia. In general, the efficacy of a 24-hour IF compared with a 16-hour type was significantly higher, without severe side effects.*

Реферат. **Клиническая характеристика цефалгий у пациентов с артериальной гипертензией при интервальном питании.** **Чунь Лю, Погорелов А.В.** *Проведено исследование эффективности и безопасности применения схем интервального питания (ИП, синонимы - периодическое, краткосрочное, лечебное голодание) у 185 пациентов в возрасте от 25 до 75 лет (средний возраст - 48,6 года) с артериальной гипертензией (АГ) и головной болью. АГ рассматривалась как наиболее вероятный фактор церебральной дисциркуляции и связанных цефалгий. Пациенты добровольно поддерживали режим краткосрочного ограничения питания сроком 16 или 24 часа 1 раз в 7 дней 4 недели. В процессе ИП 43 пациента прервало участие в исследовании, из них 31 – в 24-часовой и 12 – в 16 часовой схеме ИП. Оценка воздействия на цефалгии считалась положительной при уменьшении показателей по визуальной аналоговой шкале (ВАШ) на 2 или более баллов и / или существенного уменьшения продолжительности и частоты приступов цефалгий. При ритмичности питания с 16 часовым пропуском приема пищи положительный результат зарегистрирован у 35% (у 37,25% пациентов в молодом, 40,48% в среднем и у 28,57% пожилым возрасте) без достоверной разницы между возрастными группами. Эффективность 24-часового типа интервального питания была выше и составляла около 75% во всех возрастных группах. Негативные побочные эффекты при таком типе питания, которые требовали бы его прекращения по объективным показателям (угрожающие изменения гемодинамики,*

синкопальные состояния, другое), не были зарегистрированы, наиболее распространенной жалобой было чувство голода (от 50 до 76% в зависимости от возраста), психологическое напряжение, неопределенная тревога (в среднем около 32%). Авторы полагают, что такая психологическая особенность - а именно невозможность и нежелание переносить краткосрочное чувство голода, являлось фактором отказа от продолжения схемы лечения, и в определенных границах препятствует более широкому применению метода ИП в лечении цефалгий. В общем, эффективность 24-часового ИП по сравнению с 16 - часовым типом ИП была статистически выше, без существенных побочных эффектов.

Almost every person experiences episodes of short-term headache (HA) and in 50% of the adult population they occur systematically [2]. Headache is a consequence of many factors. The most common types of headache are primary: migraine, headache of tension, cranial neuralgia (neuropathy, pain syndromes of the cranial nerves lesions) and other headaches [2]. Secondary types of HA include those associated with head and / or neck injuries due to vascular or non-vascular disorder, associated with drug taking or its withdrawal, due to infection, homeostasis disorder, disorders in the skull, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial structure, due to mental disorders. Secondary types of headache, in particular, vascular, liquor-hypertensive, post-traumatic and others can be an indicator of life-threatening illness and require immediate examination and treatment [2, 8-9].

The influence of nutritional factors on headache was studied mainly in relation to migraine, especially as a possible trigger of an attack [6, 10]. So, alcohol (especially red wine and beer), chocolate, caffeine, cheese, preservatives for food products with nitrates and nitrites, sodium glutamate (MSG) and artificial sweeteners were identified as migraine triggers with a rate of 10 to 64% depending on the population and research methodology. In vascular types of headache the study of triggers is not relevant, in contrast to the nature and rhythm of nutrition. At present, there are known data associating short-term starvation (synonyms - interval feeding (IF), intermittent fasting) and normalization of many physiological parameters, body mass with reduction of cephalalgias vascular by type [1, 3-5, 7-8, 10], which is relevant and considered as an alternative therapy with a low risk. It is known that in laboratory rats IF or food intake restrictions cause a beneficial effect on functional results in experimental models of a broad spectrum of age-related disorders, including diabetes, cardiovascular disease, cancer and neurological disorders such as Alzheimer's disease, Parkinson's disease, and stroke [1, 4, 8]. Study of IF, for example, energy reduction by 60% for 2 days a week or in one day and feeding limited by the time of (TRF; daily food intake restriction) in people with normal weight and overweight has shown efficacy in weight loss [5] and improvement of such health indicators as insulin

resistance and decrease in risk factors for cardiovascular disease [1-2, 4, 8]. Randomized controlled clinical trials of IF versus PF and isoenergetic continuous energy restriction in humans have identified some benefits of IF for the improvement of overall health, as well as for the prevention and treatment of major diseases of aging [9]. The lack of clinical studies on the effects of PF, associated with the psychological, economic factors, relative complexity of realization and control of IF, determines actually insufficient information in this area. The relevance of the study is based on the set facts and provisions.

The purpose of the work is to evaluate clinical efficacy and negative effects during interval feeding (restriction of food intake for 16 and/or 24 hours) in cephalgia in patients with arterial hypertension.

MATERIALS AND METHODS OF RESEARCH

There was performed an examination of 185 patients aged 25-75 years (mean age – 48.6 years) with arterial hypertension I and II degree and headache, which was not due to other proven factors. All examined voluntarily supported a short-term dietary restriction for 16 or 24 hours 1 time in 7 days for a period of 4 weeks. Of 185 participants of the study, 43 refused to continue IF. Thus, the final number of participants was 142 for both 16 hours' and 24 hours' period of IF. The control group consisted of 38 men and 34 women of comparable age (mean age – 47.2 years) without arterial hypertension with episodic non-local headache, which cannot be classified as primary, at most 1-2 times a month. Inclusion criteria were consistent with ICHD-3 criteria [2]: headache is due to cerebral vascular disorders, including arterial and venous disorders, and may also be associated with arterial hypertension ICHD-3 [2].

The classification of hypertension was in line with the clinical guidelines of the Hypertension Guidelines ACC/AHA [9]. Exclusion criteria: diabetes type 1-2, secondary types of hypertension and hypertension of III degree and conditions defined as acute strokes, structural pathology of blood vessels, hemorrhages and hereditary syndromes of cephalgia, described in paragraphs 6.1.1-6.2 of ICHD-3 respectively [17]. The degree of cephalgia is evaluated according to the generally accepted visual analog scale (VAS). In the evaluation of the neurological

condition, the procedure for the diagnosis of headache, recommended by headache association [9] based on anamnesis: beginning, previous attacks and progression of symptoms, duration of attacks (up to 3 hours, more than 4 hours, continuous) and the number of days per month or week was used; preliminary treatment in acute episode and prophylactic one, response to treatment, side effects were evaluated. There was evaluated localization (one-sided, bilateral, frontal, periorbital, occipital, association with cervical pain); related symptoms (nausea, vomiting, photophobia, phonophobia, conjunctival injection or rhinorrhea); provocative factors (stress, posture, cough, load, neck tension during movement, jaundice, etc.); the severity of the pain and the effect on the activity, as well as the conditions that may affect the choice of treatment (insomnia, depression, anxiety, hypertension, asthma and heart disease, or stroke). Screening neurological examination included a general assessment of the mental status; cranial nerves, pupil, visual fields, mimic muscles, muscle strength estimation, presence of paresis of extremities, symmetry of reflexes, coordinating sphere, evaluation of moves, including tandem gait. An additional study was conducted including ultrasound dopplerography of the major arteries of the head and neck, electroencephalography, induced activity and neuropsychological examination. In this

paper the results of clinical studies, the results of paraclinical studies and the correlation between the obtained data are presented in subsequent publications due to the volume of such data. Initial processing of the obtained data was carried out using descriptive statistics with the presentation of results for quantitative characteristics in the form of the number of observations (n), the arithmetic mean (M), the standard error of mean (m), standard deviation (s); for qualitative signs in the form of relative indicators – intensive and extensive, expressed in $\% \pm m$ (standard error), visibility indicators. Comparison of statistical characteristics in different groups and in the dynamics of observation was carried out using parametric and nonparametric criteria (taking into account the data distribution law defined by the Kolmogorov-Smirnov criterion): estimation of the probability of differences in mean for unrelated and related samples – according to the relevant criteria of the Student (t).

RESULTS AND DISCUSSION

In analyzing the results, there was assessed both the impact of IF on cephalgia in the subject group and for identification of the peculiarities of the impact depending on the individual characteristics (age, sex, BMI excess, degree of hypertension, etc.). These data are presented in Table 1.

Table 1

Distribution of patients of subject group by age, AH degree and BMI, n=142

Age of patients	Total n=142	Men, n=69	Of them with BMI>N; n=49	Women, n=73	Of them BMI>N; n=58	AH 1 n=142	AH 2 n=142
25 – 44	51	29	22	22	17	38	13
%	35.92	42.03	44.9	30.14	29.31	26.79	9.15
$\pm m$	4.03	5.94	7.11	5.37	5.98	3.72	2.42
45 – 59	42	21	14	21	18	16	26
%	29.58	30.43	28.57	28.77	31.83	11.27	18.31
$\pm m$	3.83	5.54	6.45	5.30	6.07	2.65	3.25
60-75	49	19	13	30	23	14	35
%	34.51	27.54	26.53	41.10	39.66	9.86	24.65
$\pm m$	3.99	5.38	6.31	5.76	6.42	2.50	3.62
Total	142	69	49	73	58;	68	74
		48.59%	71.01%	51.41%	79.45%	47.9%	52.1%
		4.19	5.46	4.19	4.73	4.19	4.19

At the age of 25-44 there were 51 (35.9%±4.03) patients, of which 29 (42.0%±5.9) – men and 22 (30.14%±5.37) – women. At the age of 45-59, there were 42 (29.58%±3.83) patients, of which 21 (30.43%±5.54) – men and 21 (28.77%±5.30) – women. At the age of 60-75 there were 49 (34.51%±3.99) patients, of which 19 (27.54%±5.38) – men and 30 (41.1%±5.76) – women. Consequently, all groups according to the age distribution of the WHO were evenly represented by the number [***]. Given that there is evidence of a significant effect of overweight on the development of hypertension, data are presented on the quantitative distribution of patients with an excess of the body mass index (BMI). So, at the age of 25-44, among men there were 22 (44.9%±7.11); from 45 to 59 years old – 14 (28.57%±6.45); 60-75 years old – 13 (26.53%±6.31). Number of women

with BMI at the age of 25-44 was 17 (29.31%±5.98); at the age of 45-59 years old – 18 (31.83%±6.07); at the age of 60-75 years old – 23 (39.66%±6.42). The comparison between women with excess BMI and men did not show a significant difference in each age subgroup (criterion $t > 0.05$), while the percentage of women with excess BMI was higher in those aged 60-75 (39.66% versus 27.54), and in men – at the age of 24-44 years (44.9% to 29.31% without statistical significance of the difference).

According to the study, patients gave consent and participated in an interval 16-hours' and/or 24-hours' food intake, or so-called interval feeding. Table 2 shows the distribution of patients according to the dynamics of cephalgias (by this is meant positive dynamics estimated by VAS more than 2 points) at 16-hours' and 24 hours' IF.

Table 2

Distribution of patients by dynamics (decrease in HA yes /no) with IX during 16 and 24 hours

	1 week			1+2 week			1+2+3 week			1+2+3+4 week			P1	P2
	N	%	±m	N	%	±m	N	%	±m	N	%	±m		
25-44 years; n= 51;16 h	6	11.76	4.51	8	15.69	5.09	14	27.45	6.25	19	37.25	6.77	p<0.05	p<0.05
45-59 years; n=42; 16 h	9	21.43	6.33	12	28.57	6.97	13	30.95	7.13	17	40.48	7.57	p<0.05	p<0.05
60-75 years; n= 49;16 h	7	14.29	5.0	9	18.37	5.53	11	22.45	5.96	14	28.57	6.45	p<0.05	p<0.05
Total, n=142 (16 h)	22	15.49	3.04	29	20.42	3.38	38	26.76	3.72	50	35.21	4.01	p<0.05	p<0.05
25-44 years; n= 51 (24 h)	13	25.49	6.10	13	25.49	6.10	26	50.98	7.0	38	74.51	6.10		p<0.05
45-59 years; n=42; (24 h)	9	26.19	6.78	10	23.81	6.57	25	59.52	7.57	32	76.19	6.57		p<0.05
60-75 years; n= 49; (24 h)	7	14.29	5.0	9	18.37	5.53	29	59.18	7.02	37	75.51	6.14		p<0.05
Total, n=142;(24 h)	29	20.42	3.38	31	21.83	3.47	80	56.34	4.16	107	75.35	3.62		p<0.05

Note: P1) – P between 16-24 hours' course of IF relatively 4th week; P2) between 1st-4th weeks

By the results presented in Table 2, an increase in the number of headache patients who reported on the decrease in this complaint (HA manifestations) was determined, depending on the number of repetitions of IF with significant differences between the 1st episode of skipped meals and the 4th one with a close to linear dependence of the growth of the effectiveness of this method. This dependence was characteristic for all investigated age segments, without a significant difference between the young and the elderly. At the same time, the increase in the clinical effect was slowed down at the first stages of IF for patients of older age (14.29% for aged 60-75

years of 24-hours' fasting versus 25.49% for aged 25-44 years).

According to the table 3 it is possible to note the fact that IF in a 24-hours' regime was not accompanied by significant objective symptoms - side effects. The most frequent was the feeling of hunger (from 50.1% to 76.2% at the age of 45-59 years) and uncertain, indistinct anxiety (37.25% at the age of 25-44, 28.57% and 31.69% in older age groups), while the authors point out that in the repeat of IF this subjective complaint decreased by frequency and severity. Among the objective symptoms, the instability of BP of a peculiar nature

was registered, without a definite increase in the values of blood pressure or hypotension, with fluctuations within the functionally acceptable range, and did not require additional drug therapy. Suppose that this kind of instability of BP may be

due to psychological factors and at the same time related to mechanisms of anxiety as a stress-reactive type of response. As in any study, in this group there was a contingent of patients who refused to continue IF. Data on this subgroup are given in Table 4.

Table 3

Incidence of side effects in PF depending on age of study subjects

Subtypes II /age	25-44 n=51			45-59 n=42			60-75 n=49			Total n=142		
	N	%	±m	N	%	±m	N	%	±m	N	%	±m
Feeling of hunger	26	50.98	7	32	76.19	6.57	21	42.86	7.07	79	55.63	4.17
Anxiety	19	37.25	6.77	12	28.57	6.97	14	28.57	6.45	45	31.69	3.9
General weakness	18	35.29	6.69	19	45.24	7.68	28	57.14	7.07	65	45.77	4.18
Sensation of head noises, ringing	15	29.41	6.38	12	28.57	6.97	18	36.73	6.89	45	31.69	3.9
Sleep disorders	12	23.53	5.94	15	35.71	7.39	16	32.35	6.7	43	30.28	3.86
BP instability	12	23.53	5.94	16	38.1	7.49	17	34.69	6.8	45	31.69	3.9
Headache	9	17.65	5.34	8	19.05	6.06	14	28.57	6.45	31	21.83	3.47
Sensation in the stomach area	5	9.8	4.16	8	19.05	6.06	7	14.29	5	20	14.08	2.92
Paresthesias in the limbs	4	7.84	3.76	6	14.29	5.4	5	10.2	4.32	15	10.56	2.58
Dizziness	3	5.88	3.29	7	16.67	5.75	9	18.37	5.53	19	13.38	2.86
Dysphoria	3	5.88	3.29	3	7.14	3.97	4	8.16	3.91	10	7.04	2.15
Nausea	2	3.92	2.72	2	4.76	3.29	4	8.16	3.91	8	5.63	1.93
Shakiness	2	3.92	2.72	3	7.14	3.97	4	8.16	3.91	9	6.34	2.04
Salivation	2	3.92	2.72	2	4.76	3.29	3	6.12	3.42	7	4.93	1.82
Hand tremor	2	3.92	2.72	4	9.52	4.53	5	10.2	4.32	11	7.75	2.24
Sweating	1	1.96	1.94	2	4.76	3.29	5	10.2	4.32	8	5.63	1.93

Based on the analysis of the number and distribution of patients' refusal to continue IF, a relatively small proportion of such patients can be noted (12 or 6.49% for a 16-hours' schedule and 31 or 23.24% for a 24 hours' one). The most common cause, according to patients, was a feeling of hunger. Discussion of why, for a defined proportion of patients, such a feeling is inappropriate to such an extent that recognizing the benefits of treatment, declaring it to be refused, is likely to be the subject of further research that borders on medical, social psychology and neuropsychology. For practical application of IF method it is possible to use methods of rational psychotherapy, explanatory

work and rational motivation to reduce such cases of refusal to care. At the same time, we believe that this particular psychological peculiarity – namely the impossibility and unwillingness to tolerate even a short-term hunger – is a factor that prevents widespread use of IF as a treatment method. The authors are aware that headache is a result of complex hemodynamic, liquor-dynamic, neuro-dynamic processes as a subjective manifestation of real processes. Definition of such changes in the functioning of these systems during IF, doubtless, should be the subject of additional research in the specified area.

Table 4

Rate of refusals (n=185) of continuation of PF in IF

	1 st week			2 nd week			3 rd week			4 th week			Total		
	N	%	±m	N	%	±m	N	%	±m	N	%	±m	n	%	±m
16 hours n = 185	8	4.32	1.50	1	0.54	0.54	2	1.08	0.76	1	0.54	0.254	12	6.49	1.81
24 hours n=185	14	7.57	1.94	8	4.32	1.50	4	2.16	1.07	5	2.70	1.19	31	16.76	2.75
Total	22			9	4.86	1.58	6	3.24	1.30	6	3.24	1.30	43	23.24	3.11

CONCLUSIONS

1. Adherence of patients with cephalgia and hypertension to a rhythmic diet with a 16-hours' interval in food intake with repeat 1 time in 7 days was accompanied by an abatement of headache in severity, duration and frequency in 35.21% in general (37.25% of young, 40.48% - of average and 28.57% - of elderly age patients) without a significant difference between age groups. The effectiveness of a 24-hours' type of intermittent fasting was higher, overall effectiveness was about 75% in all age groups.

2. Negative side effects of a short-term interval in food intake, which required cessation by objective findings (threatening changes in blood pressure, syncope states, and others), were not recorded, while

part of the study group informed of feeling of hunger (from 50 to 76% with a difference by age), psychological tension, uncertain anxiety (on average about 32%), especially before the first skipped meals. For subjective reasons 16.76% of subjects stopped a 24-hours' and 6.49% of those - a 16-hours' IF.

3. Generally, the efficacy of a 24-hours' IF by the criterion of decrease in the intensity and / or duration / incidence of cephalgia compared with a 16-hours' type of IF was statistically higher without significant side effects, which makes it possible to characterize the method as safe in all age groups with an efficacy of up to 75% in cephalgias caused by cerebral discirculation in patients with arterial hypertension.

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