Original Research Article

Treatment of migraine headache with Migracorb, caffeine and ascorbic acid combination

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ABSTRACT

The migraine mechanism; the release of inflammatory neuropeptides, nuclear factor (NF-kB) and proinflammatory proteins leads to increase blood vessel permeability, tissue edema and pain sensitization. From 1989 to 2013 in a single blind randomized clinical trial conducted in Shiraz central hospital, 700 cases (460 females and 240 males) with the diagnosis of moderate to severe pain intensity migraine were enrolled. The cases (n=350) were put on vitamin C (ascorbic acid) 25 mg in a capsule mixed in a cup of tea (100 ml) containing about 20 mg caffeine (Migracorb), to drink three times per day with sugar. The controls (n=350) drank three times per day with sugar. 22 % of the female cases and 7.5 % of the male cases had abortive response to Migracorb from 10 min to 3 h. 53 % of the female cases and 39 % of the male cases were cured by taking Migracorb after 6 months. Only 0.5 % of the female control group cases were cured after 6 months.

The combination of vitamin C as antioxidant and caffeine as anti-inflammation cured a significant number of patients with migraine headache.

***Keywords*:** Migraine headache, vitamin C, caffeine

INTRODUCTION

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. Typically the headache affects one half of the head, is pulsating in nature, and lasts from 2 to 72 h. Associated symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell. Up to one-third of people with migraine headaches perceive an aura: a transient visual, sensory, language, or motor disturbance which signals that the headache will soon occur (classic migraine), migraine without aura is called common migraine.

The exact mechanisms of migraine are not known. It is, however, believed to be a neurovascular disorder [1]. The primary theory is related to increased excitability of the cerebral cortex and abnormal control of pain neurons in the trigeminal nucleus of the brainstem [2] .

There are three main aspects of treatment: trigger avoidance, acute symptomatic control, and pharmacological prevention [1]. Preventive migraine medications are considered effective if they reduce the frequency or severity of migraine headache attacks by at least 50 % [3].

In this study, we evaluated the preventive and especially, curative effect of Migracorb (caffeine and ascorbic acid combination) in patients with migraine headache in the past 24 years.

MATERIALS AND METHODS

From 1989 to 2013 in a single blind randomized clinical trial conducted in Shiraz central hospital, in Shiraz, 700 subjects with the diagnosis of chronic moderate to severe migraine headache, common and classical, according to the international headache society diagnostic criteria, were enrolled.

Interviews were conducted directly with the subjects, and verbal consent was obtained. Cases and controls were interviewed and were asked to answer a questionnaire which contained detailed information on sociodemographic characteristics (including age, sex, place of residence), occupation, familial history of headache, and medical history about presenting disease (including the severity of the pain, duration of the headache, frequency of attacks, triggers, and type of treatment). They were on different types of anti- migraine medications, with poor response. And they were asked to stop their migraine therapy (beta- blockers was tapper of in one month) before enrolling for the present study.

Patients were stratified based on sex (460 females and 240 males). Then they were randomly allocated into two groups by block randomization. The cases (n=350) and the

controls (n=350) were treated as out-patients. Patients were prescribed vitamin C (ascorbic acid) 25 mg in a capsule to be mixed in a cup of tea (100 ml) (containing about 20 mg caffeine) to drink three times per day with sugar. Vitamin C tablets (250 mg) were grinded to powder and were put in capsules. The controls mixed a capsule of sugar with tea to drink three times per day with sugar. The cases and controls did not know whether they were in the treatment or placebo groups. The subjects were followed up every three months for the first year and every six months after. The duration of follow up was from 10 to 24 years (median 15 years).

Analysis was conducted to compare the response to therapy. Standard statistical procedures were carried out using SPSS software (version 21, Chicago, IL, USA). Quantitative and categorical variables were compared between cases and controls by Student t- test and Chi- Square test, respectively. Two sided p values were considered statistically significant at the 0.05 level.

RESULTS

Of all eligible subjects, 350 controls and 350 cases were included in this study. Of all subjects 460 (66 %) were female and 240 (34 %) were male. Comparison of the characteristics of migraine headache was compared between cases and controls and shown in table 1.

In female cases 192 (83 %) had common migraine and 38 (17 %) had classical migraine. In the female control group 195 (85 %) and 35 (15 %) had common and classical migraine, respectively. In male cases 92 (77 %) and 28 (23 %), and in the male control group 96 (80 %) and 24 (20 %) had common and classical migraine, respectively. Age range in the female cases was from 11 to 65 years and in the male cases was from 7 to 60 years. In the female control group age range was from 10 to 67 and in the male control group it was from 7 to 58 years. Mean age of male patients in the control group was significantly higher than in the case group (34.61± 11.77 and 30.46 ± 13.54). Also in males, frequency of attacks was significantly higher in controls than cases (4.63 ± 7.46 and 2.99 ± 1.98). In females, both days before and with men were significantly higher in cases than controls (3.43 ± 1.79 and 2.88± 1.25) and (3.14 ± 3.04 and 2.6 ± 1.5), respectively. All other evaluated variables were comparable between the two groups.

In table 2 the most used therapy by the cases and controls are shown. Propranolol tablets were used regularly by 56 (24 %) of the female cases and 19 (16 %) of the male cases.

It was used by 53 (23 %) of the female control group and 15 (12.5 %) of the male control group. It should be mentioned that both the case and the controls were using different types of therapies with pain attacks.

With regards to response to therapy, 50 (22 %) of the female cases and 9 (7.5 %) of the male cases had abortive response to Migracorb in 10 min to 3 h (median, 30 min), and none of the controls had such a response. One hundred twenty three (53 %) of the female cases and 47 (39 %) of the male cases were cured by taking Migracorb three times per day, after an interval of 3 to 12 months (median, 6 months). Only one (0.5 %) of the females in control group was cured after 6 months for both female and male groups.

In the control group 56 (24 %) and 2 (2 %) of the females and males had decreased intensity and duration, and increased intervals of the headache attacks. It was in 21 (9 %) and 19 (16 %) of the female and male cases respectively for females and for males. From 3 months to 10 years (median, 6 months) after discontinuation (D/C) of Migracorb, 27 (12 %) of the female cases and 9 (7.5 %) of the male cases had relapse of migraine headache. Two (1 %) of the females of the control group had relapse of headache 6 months after D/C of placebo. Twenty-three (10 %) of the female cases and 17 (14 %) of the male cases had relapse of headache after 6 months-2 years (median, 12 months) of being on Migracorb. Three (1.5 %) of the women in the female control group had relapse at the same time. Thirty-six (16 %) of the female cases and 28 (23 %) of the male cases had no response to Migracorb after 6 and 12 (median, 9) months of therapy.In the control group 168 (73 %) of the females and 118 (98 %) of the males did not respond to therapy during the same interval (table 3).

Table 1. The characteristics of patients with migraine headache in Shiraz- Iran (1989-2013)

	Cases			**Controls**			**P value**
		Classical	**common**		**Classical**	**Common**	
Female, No. (%)	230 (66)	38(17)	192(83)	230	35(15)	195(85)	0.798
Male	120 (34)	28(23)	92(77)	120	24(20)	96(80)	0.638
Total	350 (100)			350			
Age, year Mean (SD) Females	33.77 (± 11.41)			34.37 (± 11.24)			0.570

Males	30.46 (± 13.54)	34.61 (± 11.77)	0.011*
History of having headache, year			
Mean (SD)			
Females	8.14 (± 6.63)	7.20 (± 5.88)	0.223
Males	8.57 (± 7.50)	8.91(± 7.07)	0.783
Duration of headache attacks, hour			
Mean (SD)			
Females	43.18 (± 34.45)	41.52 (± 27.23)	0.727
Males	23.70 (± 16.80)	20.65 (± 18.68)	0.184
Frequency of attacks (six per month to one every 3 months)			
Mean (SD)			
Females	3.97(± 3.86)	4.20 (± 4.10)	0.680
Males	2.99(± 0.48)	4.63 (± 4.46)	0.020*
Nausea, No (%)			
Females	185(80)	180(78)	0.680
Males	98(82)	100(83)	0.972
Vomiting			
Females	117(51)	120(52)	0.903
Males	62(52)	59(49)	0.737
Sensitivity to light (photophobia)			
Females	121(53)	116(50)	0.582
Males	60(50)	64(53)	0.737
Sensitivity to smells			
Females	95(41)	91(40)	0.901
Males	46(38)	47(39)	0.978
Sensitivity to sound (phonophobia)			
Females	165(72)	170(74)	0.705
Males	88(73)	85(71)	0.840
Pulsatile			
Females	216(94)	210(91)	0.296
Males	115(96)	120(100)	0.079
Scalp tenderness			
Males	37(31)	35(29)	0.843
Eye pain			
Females	184(80)	179(78)	0.680
Males	97(81)	100(83)	0.814
Headache with menses only			
No.(%)	35(15)	23(10)	0.138

Location of headache, No.(%)				
	Females	Males	Females	Males
Always right frontal	14(6)	3(2.5)	10(4)	3(2.5)
Always left frontal	36(16)	12(10)	30(13)	12(10)
Right or Left frontal	136(59)	75(63)	132(57)	75(63)
Bilateral frontal/temporal	27(12)	24(20)	48(21)	18(15)
Total	213	114	220	108
Positive family history				
Total	150(65)	104(88)	149(65)	101(86)
Headache decreased with sleeping				
	172(75)	90(75)	180(78)	88(73)

Table 2. The most used medications by patients with migraine headache

	Cases, No (%)		**Controls**	
	Females	Males	Females	Males
Analgesics	44(19)	36(30)	53(23)	25(21)
Propranolol	56(24)	19(16)	53(23)	15(12.5)
Amitriptyline	32(14)	9(7.5)	29(13)	-
Ergotamines, oral	52(23)	30(25)	47(20)	63(52.5)
Sumatriptan, oral	30(13)	-	24(10.5)	-
Diazepam, IM	12(5)	9(7.5)	24(10.5)	17(14)
Topamax (Topiramate)	4(2)	17(14)	-	-
total	230	120	230	120

No: Number; IM: Intramuscular

Table 3: Response to Migracorb (Caffeine and ascorbic acid combination) versus placebo in patients with migraine headache after 10 to 24 years (median, 15) of follow up

	Females, No (%)		**Males No (%)**	
	N=230 n=230		N=120	N=120
	Case	Control	Case	Control
Cured, after 3-12 (median =6) months of daily usage (three times per day)	123(53)	1(0.5)	47(39)	-
P value	<0.001		<0.001	
intensity, duration, intervals	21(9)	56(24)	19(16)	2(2)
P value	<0.001		0.0004	
Relapsed with discontinuation (D/C) of therapy (Rx); duration of D/C Rx till relapse of headache: 3 months to 10 years (median=6 months)	27(12)	2(1)	9(7.5)	-
P value	<0.001		0.006	
Relapsed on Rx [6 months-2 years(median=12 months)]	23(10)	3(1.5)	17(14.5)	-
P value	0.0002		<0.001	
No response after 6-12 (median=9) months	36(16)	168(73)	28(23)	118(98)
P value	<0.001		<0.001	
Abortive response in 10 minutes to 3 hours (median=30 min)	50(22)	-	9(7.5)	-
P value	<0.001		0.006	

No: Number

DISCUSSION

Migraine headache is one of the most common, yet potentially debilitating disorders encountered in primary care. Approximately 18 percent of women and 6 percent of men in the United States have migraine headache, and 51 percent of these persons report reduced work or school productivity. Patients typically describe recurrent headaches with similar symptoms, and approximately one-third describe an aura preceding the headache [4].

Treating acute migraine is challenging because of substantial rates of nonresponse to medications and difficulty in predicting individual response to a specific agent or dose [5].

Preventive migraine medications are considered effective if they reduce the frequency or severity of the migraine attacks by at least 50 % [3]. Topiramate, divalproex, sodium valporate, propranolol, metoprolol, gabapentin, timolol, hormone therapy [6], frovatriptan (for menstrual migraine), amitriptyline, venlafaxine, angiotensin converting enzyme inhibitor or angiotensin II receptor antagonist, warfarin [7], botox (effective in prevention of chronic migraines but not episodic ones) [8,9], acupuncture, chiropractic manipulation, physiotherapy, massage and relaxation, butterbur (Petasiteshypridus), neurostimulation, transcutaneous electrical nerve stimulation [10], and finally migraine surgery, which involves decompression of certain nerves around the head and neck, are other preventive measures.

Abortive therapy should be used as early as possible after the onset of symptoms. Effective first- line therapies for mild to moderate migraine are nonprescription nonsteroidal anti-inflammatory drugs and combination analgesics containing acetaminophen, aspirin, and caffeine (Excedrin Migraine) [5].

Selective serotonin (5- hydroxytryptamine[5-HT]) receptor agonists that activate 5-HT_1B and 5-HT_1D (5 $HT_1B/_1D$) receptors are known as the triptans. They are considered first-line therapy for moderate to severe migraine or mild to moderate attacks unresponsive to nonspecific analgesics [11,12]. The vasoconstrictive properties of triptans preclude their use in patients with ischemic heart disease, stroke, uncontrolled hypertension, or hemiplegic or basilar migraine [13].

Combination of triptans with selective serotonin reuptake inhibitors (monoamine oxidase inhibitors) could lead to serotonin syndrome, a potentially life-threatening condition characterized by altered mentation,

autonomic instability, diarrhea, neuromuscular hyperactivity, and fever [11]. Ergotamines and dihydroergotamineare are migraine-specific drugs that bind to serotonergic receptors. Little evidence supports the use of oral ergotmines. Poor absorption and high rates of adverse events preclude their use in most situations. Combination of ergotamine and caffeine (Cafergot) may have fewer adverse effects than pure ergotamines.

Other effective therapies include antiemetics, dexamethasone, isometheptene-compounds, lidocaine, barbiturate-containing analgesics, calcitonin gene-related peptide antagonist, and transcranial magnetic stimulation [5].

Several theories regarding the migraine mechanism have been proposed. According to the neurogenic inflammation theory of migraine, release of inflammatory neuropeptides, like substance P, neurokinin A, and calcitonin gene-related peptide (CGRP) from the trigeminal sensory afferent onto the dura could act on vascular tissue to cause the components of neurogenic inflammation; vasodilation, plasma protein extravasation in the surrounding area, endothelial cell changes, platelet aggregation and subsequent release of serotonin and other mediators, white cell adhesion and subsequent inflammation [14]. Vasoconstrictive acute therapeutic agents like ergotamines and triptan also inhibit release of inflammatory neuropeptides [15].

In 1986 Sen and Baltimore discovered several nuclear factors that interact with the immunoglobulin – enhancer sequences. One factor, initially detected in B cells, was associated with the kappa light chain enhancer and was therefore called NF-κB [16]. NF-κB can be activated by a wide variety of agents that either signal or are themselves a threat to the organism: TNFα, IL-1, lipopolysaccharides, several viruses and double–stranded RNA. These agents induce a cascade of events leading to the phosphorylation of the inhibitor of NF-κB (IκB) and its further degradation. As a consequence, the P50-RelA heterodimer is released from its cytoplasmic anchor and translocate into the nucleus, where it binds to different gene promoters, thus inducing the transcription of a large number of genes such as those encoding IL-6 and several adhesion molecules. NF-κB is a privileged mediator of the immune and inflammatory responses and of the acute phase response [17].

The expression of these and probably other proinflammatory proteins leads to increase blood vessel permeability, tissue edema, and pain sensitization, providing in part of molecular and functional mechanisms for migraine pathogenesis in the dura mater [18].

The activity of NF-κB is clearly under the control of an oxidant and antioxidant balance. The level of free radicals withstood by a cell directly depends on the level of the antioxidant defenses and includes nonenzymatic defenses (glutathione, vitamin E and C) and three main antioxidant enzymes: superoxide dismutase, catalase-destroying H_2O_2 and glutathione peroxidase [19].

Migraine may be considered a complex regional pain syndrome (CRPS) of the brain, with neurogenic inflammation, where the release of neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) produce reactive oxygen species (ROS), which in turn cause tissue damage and microvascular dysfunction [20,21] .In support of this theory, increased levels of SP, CGRP, and ROS have been found in both CRPS and migraine [22].

Vitamin C, produced by neurogenic inflammation during early stages of CRPS [23]. A small nonrandomized trial of a mixture of antioxidants, and a randomized controlled trial of the antioxidants; pine bark extracts and vitamins C and E, reported significantly improved migraine outcomes [24.25].

The effect of tea is most probably due to the caffeine it contains. Caffeine is a receptor antagonist at all adenosine receptor subtypes of the central nervous system. Antagonism at these receptors stimulates the medullary vagal, vasomotor, and respiratory centers, which increases respiratory rate, reduces heartrate, and constricts blood vessels. Caffeine, like other xanthines, also acts as a phosphodiesterase inhibiter. As a competitive nonselective phosphodiesterase inhibitor, caffeine raises intracellular c AMP, activates protein kinase A, inhibits TNF-alpha and leukotriene synthesis, and reduces inflammation and innate immunity.

CONCLUSION

In our randomized case-control study of patients with long-term history of migraine with and without aura who had failed to respond to multiple treatments of beta-blockers, antidepressants, anticonvulsants, or 5-HT receptor agonists (table 2), were put on the combination of antioxidant vitamin C, and vasocontstirictive caffeine in tea.

The synergistic effect of these two compounds may have protected the cells from oxidative stress, and subsequently reduced headache frequency and severity and even cure a significant number of patients 123 (53 %) of the females and 47 (39 %) of the male cases). In the control group only one (0.5 %) female patient was cured.

It seems that the combination of vitamin C and caffeine; as antioxidant, anti-inflammation and vasocontrictive could prevent proinflammatory proteins expression and activation, and resulted in cure of a significant proportion of patients with migraine headache. This complex should be taken three times per day.

Twenty seven (12 %) female and 9 (7.5 %) of the male cases had relapse of recurring headaches 3 months to 10 years after discontinuation of therapy. Twenty-three (10 %) of the female and 17 (14 %) of the male cases had relapse of the headache on therapy, after 6 months to 2 years (median, 12 months). And 36 (16 %) of the female and 28 (23 %) of the male cases had no response to this complex after 6 to 12 months (median, 9 months). So if a patient had no response to this combination after 12 months, there is no hope for any effect.

Instead of vitamin C tablets, patients could mix lemon/Limes-juice (10 ml) (containing about 15 mg of vitamin C) in a cup of tea, about 100 ml (containing 20 mg of caffeine), and could drink with or without sugar, three times per day.

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