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Acupuncture decreases matrix metalloproteinase-2 activity in patients with migraine

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ABSTRACT

Objective To evaluate the effect of acupuncture on the serum matrix metalloproteinase-2 (MMP-2) level and activity in patients with migraine.

Methods After baseline testing, eligible patients with migraine according to the criteria of the International Headache Society who volunteered to join the study were included (n=27). The patients received 10 sessions of acupuncture treatment. The points selected were bilateral ST8, ST44, LI4, LI11, LIV3, SP6, GB1, GB14, GB20, GV14, GV20, *Yintang*, *Taiyang* and ear *Shenmen*. Pain was measured using a visual analogue scale (VAS). Short form-36 (SF-36) was used to determine their quality of life. Blood samples were taken before treatment and after the first and last sessions of acupuncture for measurement of MMP-2 concentration and activity.

Results The mean VAS was 85.5±16.6 before acupuncture and was significantly decreased to 39.8±20.6 after 10 sessions of acupuncture (p<0.0001). There was a significant increase in all SF-36 scores after acupuncture compared with values before treatment (p<0.0001). No significant differences were found in MMP-2 concentrations before treatment and after the first and last sessions (p>0.05). However, there were significant changes in MMP-2 activity (p<0.0001).

Conclusions The results of this study showed a clinically relevant decrease in MMP-2 activity in patients with migraine treated with acupuncture. The mechanism underlying the effect of acupuncture in alleviating pain may be associated with a decrease in MMP-2 activity.

INTRODUCTION

Migraine is one of the most common neurological disorders. It is described by unilateral throbbing headaches with or without aura, and characterised by attacks.^{1–3} The current global prevalence of migraine is 10%. It is more common among women and between the ages of 25 and 55.¹ Approximately 6–8% of men and

16–18% of women in America are estimated to suffer from migraine.^{2 4 5}

Acupuncture is a method of treatment that has been used for thousands of years for a range of conditions.⁶ It is a treatment modality frequently employed in migraine and is known to be effective.⁷ The mechanism by which it exhibits its effect has not yet been fully clarified, and various mechanisms have been proposed. It has been suggested that the needles stimulate A delta fibres, closing the 'pain gates' in the CNS so pain is not perceived since the stimuli fail to reach the thalamus.⁸ The mechanisms of the analgesic effects of acupuncture involve endogenous opioids (β-endorphin, enkephalin, endomorphin, dynorphin) as well as serotonin.⁹

It has been suggested that pain in migraine occurs as a result of vasodilation in the intracranial vessels or release of vasoactive peptides as a result of activation of the perivascular fibres of the trigeminal nerve.¹⁰ An increase in the concentration and activity of matrix metalloproteinase (MMP) in the pathogenesis of migraine has recently been proposed. MMPs are neutral proteases responsible for the proteolytic activity of extracellular matrix proteins. An increase in MMP production is known to result in tissue injury and inflammation. Structures constituting the blood barrier in the brain contain extracellular matrix molecules, the substrate for MMPs (particularly MMP-2 and MMP-9). With increased MMP activity, the permeability of the blood–brain barrier is compromised, and headache occurs with pain-sensitive meningeal structures being affected.^{11 12} The proteolytic activities of MMPs released in the form of inactive zymogens are inhibited by specific tissue inhibitors (TIMP). Studies have shown increases in favour of MMP in the MMP/TIMP ratio in



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migraine.¹³ Studies have also shown that acupuncture reduces MMP expression in some inflammatory diseases, such as osteoarthritis.¹⁴

This study investigated the effect of acupuncture therapy on levels and activation of MMP-2, a pathological increase in which has been shown to compromise the blood–brain barrier, in patients with migraine.

MATERIALS AND METHODS

Study design

The study was carried out between March and December 2012 at the Ataturk University Research and Practice Center for Acupuncture and Complementary Medicine, Turkey. The treatments were fully documented in accordance with STRICTA.¹⁵ Acupuncture was performed by an acupuncturist with an acupuncture practitioner licence from the Turkish Ministry of Health.

Patients

From March to December 2012 a total of 42 patients with migraine visited the Ataturk University Research and Practice Center for Acupuncture and Complementary Medicine seeking acupuncture treatment. Inclusion criteria were a diagnosis of migraine with/without aura based on the criteria of the International Headache Society.¹⁶ Exclusion criteria were an additional other type of headache, use of analgesics on more than 10 days a month, prophylactic headache treatment with drugs during the previous 4 weeks and any acupuncture treatment during the previous 1 year.

After baseline evaluation by a neurologist, eligible patients ($n=30$) were enrolled in the study. These patients received 10 sessions of acupuncture treatment for 5 weeks, two sessions a week. Three of the patients had incomplete MMP-2 data, so the results from 27 patients were used in the final analysis.

We estimated that a sample of 25 patients provided a statistical power of 90% for determining a difference in MMP-2 level of 675 ng/mL with an α error of 5%.

Intervention

Classical acupuncture points were used without a formal traditional Chinese medicine diagnosis in the acupuncture group. Neither manual needle stimulation nor moxibustion were used. Needles were stainless steel, 0.25 mm in diameter and 25 mm in length. Sterile, disposable and single-use needles were used. The depth of insertion was 0.5–1 *cun*. The needles were left in place for 30 min and *de qi* was not sought. The points selected were bilateral ST8, ST44, LI4, LI11, LR3, SP6, GB1, GB14, GB20, *Taiyang* and ear *Shenmen* and unilateral GV14, GV20 and *Yintang*. All acupuncture points were selected and localised on the basis of the WHO Standardised Acupuncture Point Location (WHO Regional Office for the Western Pacific, WHO Standardised Acupuncture

Point Location in the Western Pacific, WHO, Manila, Philippines, 2008).

Outcome measurement

Pain severity was measured using a 100 point visual analogue scale (VAS) and Short Form-36 (SF-36) was used to determine quality of life. The data were collected at baseline and after 10 sessions of treatment. Blood samples were collected three times in order to measure the serum MMP-2 concentration and activity. The first was collected before acupuncture, the second after the first session of acupuncture and the last after all 10 sessions. Adverse events were monitored for 3 months from initial acceptance of acupuncture treatment to the end of treatment.

Biochemical analyses

Serum was separated from the blood samples by centrifugation at 5000g for 5 min at 4°C and stored immediately at –20°C until assay.

MMP-2 activity in the serum samples was determined using commercially available human Biotrak enzyme-linked immunosorbent activity assay kits (Amersham Pharmacia Biotech, Piscataway, New Jersey, USA). Total MMP-2 concentration was measured using Boster Immunoleader ELISA kits (Wuhan Boster Biological Technology, Wuhan, China). Measurements were performed in accordance with the manufacturers' instructions.

Statistical analysis

All analysis was carried out using SPSS 18 software. Numerical variables are expressed as mean \pm SD and categorical variables as n (%). Numerical data were checked for normal distribution. The t test and repeated measures analysis of variance (ANOVA) were used for comparisons. Repeated measures ANOVA with Tukey correction was performed on the averaged MMP-2 activity. Significance was set at $p<0.05$.

RESULTS

The study sample consisted of 20 women (74.1%) and 7 men (25.9%). The mean age was 32.1 ± 11.1 years. No serious adverse events were documented. Mean VAS was 85.5 ± 16.6 before acupuncture, which decreased significantly to 39.8 ± 20.6 after 10 sessions of acupuncture ($p<0.0001$). The difference in VAS scores analysed using paired comparisons was significant ($t=9.11$, $p<0.0001$). The decrease in VAS was approximately $51.2\pm25.7\%$.

There was a significant difference in all SF-36 scores after acupuncture compared with the pretreatment values ($p<0.0001$; [table 1](#)).

The mean MMP-2 concentration and activity are shown in [table 2](#). No significant differences were observed between MMP-2 concentrations before treatment, after the first session or after the last session ($p>0.05$). However, there were significant changes in

Table 1 Mean±SD Short Form-36 (SF-36) scores before and after acupuncture

	SF-36		p Value
	Before acupuncture	After acupuncture	
Physical functioning	75.3±15.1	87.5±11.7	p<0.0001
Role-physical	57.4±35.2	81.4±20.6	p<0.0001
Bodily pain	35.4±19.0	78.5±20.0	p<0.0001
General health perception	50.9±18.3	64.8±16.6	p<0.0001
Vitality	35.1±14.3	59.7±17.1	p<0.0001
Social-functioning	63.0±19.8	72.3±15.3	p<0.0001
Role-emotional	52.4±33.5	69.0±24.3	p<0.0001
Mental health	51.0±23.8	69.4±19.3	p<0.0001

mean MMP-2 activity, which decreased significantly after the first and final sessions compared with baseline values ($p<0.0001$ for both).

DISCUSSION

The results of this clinical trial indicate a significant decrease in MMP-2 activity and clinically significant improvements in VAS and SF-36 scores in patients with migraine treated with acupuncture by the end of the 10 sessions. To the best of our knowledge, this study is the first trial to investigate the effect of acupuncture on MMP-2 concentrations and activity in patients with migraine.

Clinical studies have shown that acupuncture is an effective method for treating migraine. Many trials have suggested that acupuncture plays an important role in managing pain in patients with migraine without causing any serious side effects.^{17–19}

Migraine is a chronic type of headache with recurrent symptoms that lead to a reduction in quality of life during and between crises. According to WHO, migraine alone ranks 19th among all causes of years spent with disability.^{20–21} It is very important to relieve pain and increase quality of life. In our study a decrease of more than 50% in mean VAS scores was observed in patients with migraine after 10 sessions of acupuncture treatment. Our findings are in line with previous research.²²

Migraine is caused by the release of pain-producing inflammatory substances around the cranial nerves/blood vessels.²³ MMPs are important mediators of inflammation.²⁴ Research has emphasised that increased MMP concentrations and/or activities may be associated with migraine pathophysiology.^{11–25–26} MMP-2 is

involved in the disruption of the blood–brain barrier during attacks in patients with migraine. It has been suggested that patients with increased MMP-2 levels could benefit from the use of MMP inhibitors.¹³ Several data have demonstrated that cyclo-oxygenase inhibitors have a significant inhibitory effect on the activities of MMP-2 and MMP-9.^{27–28} Cyclo-oxygenase inhibitors have an anti-inflammatory effect and are usually used in the treatment of migraine.²⁹ The anti-inflammatory effects of acupuncture have also been shown in previous studies.^{30–31} One study reported that electroacupuncture caused cyclo-oxygenase-2 inhibition and thus established an analgesic effect in the spinal dorsal horn.³¹ Chen *et al*³⁰ showed that acupuncture inhibited an abnormal increase in MMP-2 in the endometrium in rats with induced endometriosis. Acupuncture has also been shown to downregulate the expression of MMP-1 and MMP-3 in rats with induced osteoarthritis.¹⁴ The results of our study showed a decrease in MMP-2 activity in patients with migraine patients with acupuncture without a decrease in MMP-2 concentration. This suggests that acupuncture may reduce MMP-2 activity through inhibition of the inflammatory process. Although there was a decrease in MMP-2 concentration after acupuncture in our study, the difference was not significant. This may be attributed to the low sample size and number of acupuncture sessions involved. Additionally, it may be that acupuncture is unable to reduce MMP-2 synthesis, but that this treatment modality may cause anti-inflammation and relieve pain by reducing the activity of existing MMP-2 enzyme.

Altered concentrations of MMP-9 have been reported to demonstrate important pathophysiological changes in migraine and in response to drug therapy, similar to MMP-2. In the present study we did not have resources to measure MMP-9, which has been suggested to have diagnostic and prognostic value in many disease conditions. A good correlation has been shown between MMP-9, MMP-2 and TIMP-2 concentrations in serum and plasma samples.³²

An imbalance between MMPs and TIMPs has been observed in different diseases. MMP-2 activity is decreased as a consequence of increased TIMP-2 levels. This could explain our findings, because MMP-2 levels were not affected and therefore increased concentrations of the endogenous inhibitor TIMP-2 could account for the decreased MMP-2 activity. The remodelling of the extracellular matrix depends on the critical balance between MMPs and TIMPs. Changes in circulating MMPs/TIMPs concentrations are implicated in the pathophysiology of a

Table 2 Mean±SD levels of matrix metalloproteinase-2 (MMP-2) concentration and activity

	Baseline	After the first session	After the last session	p Value
MMP-2 concentration (ng/mL)	799.46±727.64	571.13±522.11	510.48±283.43	0.212
MMP-2 activity (ng/mL)	1717.34±421.25	1368.37±450.75*	1176.30±406.48*	p<0.0001

*p<0.0001 compared with baseline values.

variety of diseases.^{33 34} It is possible that increased TIMP levels affect MMP activity, and this issue should be addressed in further studies.

This study has several methodological limitations. The main limitation is the lack of a control group. Large studies with control groups including patients who are treated with sham acupuncture are needed to clarify the relation between acupuncture and MMP-2 concentrations and activity. Many drugs may affect MMP concentration/activity. In a previous study it was shown that some antihypertensive drugs may change the circulating MMP concentration.³³ It is possible that the effects of the drugs used by our patients may have altered the MMPs. This may be considered as a limitation. Also, there was no follow-up after acupuncture therapy in our trial. Further studies are required to establish possible effects of acupuncture on MMP-2 and other MMPs in migraine.

CONCLUSION

The results of this study showed a clinically significant decrease in MMP-2 activity in patients with migraine treated with acupuncture. The mechanism underlying the alleviating pain effects of acupuncture may be associated with a decrease in MMP-2 activity.

Summary points

- ▶ Matrix metalloproteinases (MMPs) are implicated in the mechanism of migraine.
- ▶ MMP-2 concentration and activity were measured before and after a course of acupuncture.
- ▶ The activity of MMP-2 was significantly reduced after treatment.

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Contributors YC performed the acupuncture. GO and MC evaluated patients before and after treatment and collected the data. EL and FA studied the blood samples. ZA analysed the data. YC prepared the article. HA and FA contributed to the text.

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Competing interests None.

Ethics approval The study protocol was approved by the ethics committee of Ataturk University Faculty of Medicine and the study was performed in compliance with the Declaration of Helsinki.

Patient consent Informed written consent was obtained from all participants.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Lipton RB, Stewart WF, Scher AI. Epidemiology and economic impact of migraine. *Curr Med Res Opin* 2001;17(Suppl 1): s4–12.
- 2 Hildreth CJ, Lynn C, Glass RM. Migraine headache. *JAMA* 2009;301:2608.
- 3 Lipton RB, Bigal ME. The epidemiology of migraine. *Am J Med* 2005;118(Suppl 1):3S–10S.
- 4 Zishan G, Xuguang L, Shuguang Y, *et al.* Electroacupuncture at acupoints reverses plasma glutamate, lipid, and LDL/VLDL in an acute migraine rat model: a 1H NMR-based metabolomic study. *Evid Based Complement Alternat Med* 2014;2014:659268.
- 5 Stovner L, Hagen K, Jensen R, *et al.* The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007;27:193–210.
- 6 Cayir Y, Engin Y. Acupuncture for primary hyperhidrosis: case series. *Acupunct Med* 2013;31:325–6.
- 7 Linde K, Streng A, Jurgens S, *et al.* Acupuncture for patients with migraine: a randomized controlled trial. *JAMA* 2005;293:2118–25.
- 8 Zhao ZQ. Neural mechanism underlying acupuncture analgesia. *Prog Neurobiol* 2008;85:355–75.
- 9 Lin J, Chen W. Acupuncture analgesia: a review of its mechanisms of actions. *Am J Chin Med* 2008;36:635–45.
- 10 Bruno PP, Carpino F, Carpino G, *et al.* An overview on immune system and migraine. *Eur Rev Med Pharmacol Sci* 2007;11:245–8.
- 11 Romi F, Helgeland G, Gilhus NE. Serum levels of matrix metalloproteinases: implications in clinical neurology. *Eur Neurol* 2012;67:121–8.
- 12 Murphy G, Nagase H. Progress in matrix metalloproteinase research. *Mol Aspects Med* 2008;29:290–308.
- 13 Goncalves FM, Martins-Oliveira A, Lacchini R, *et al.* Matrix metalloproteinase (MMP)-2 gene polymorphisms affect circulating MMP-2 levels in patients with migraine with aura. *Gene* 2013;512:35–40.
- 14 Bao F, Sun H, Wu ZH, *et al.* [Effect of acupuncture on expression of matrix metalloproteinase and tissue inhibitor in cartilage of rats with knee osteoarthritis]. *Zhongguo Zhen Jiu* 2011;31:241–6.
- 15 MacPherson H, White A, Cummings M, *et al.* Standards for reporting interventions in controlled trials of acupuncture: the STRICTA recommendations. *J Altern Complement Med* 2002;8:85–9.
- 16 Schwartz B, Stewart W, Simon D, *et al.* ICH-10 guide for headaches. *Cephalalgia* 1997;17(Suppl 19):182.
- 17 Allais G, De Lorenzo C, Quirico PE, *et al.* Acupuncture in the prophylactic treatment of migraine without aura: a comparison with flunarizine. *Headache* 2002;42:855–61.
- 18 Diener HC, Kronfeld K, Boewing G, *et al.* Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial. *Lancet Neurol* 2006;5:310–16.

- 19 Wang LP, Zhang XZ, Guo J, *et al.* Efficacy of acupuncture for migraine prophylaxis: a single-blinded, double-dummy, randomized controlled trial. *Pain* 2011;152:1864–71.
- 20 Ferracini GN, Dach F, Speciali JG. Quality of life and health-related disability in children with migraine. *Headache* 2014;54:325–34.
- 21 World Health Organization. Headache disorders. 2014. <http://www.who.int/mediacentre/factsheets/fs277/en/> (accessed 8 May 2014).
- 22 Linde K, Allais G, Brinkhaus B, *et al.* Acupuncture for migraine prophylaxis. *Cochrane Database Syst Rev* 2009;(1):CD001218.
- 23 Pietrobon D, Moskowitz M. Pathophysiology of migraine. *Annu Rev Physiol* 2013;75:365–91.
- 24 Lagente V, Boichot E. Role of matrix metalloproteinases in the inflammatory process of respiratory diseases. *J Mol Cell Cardiol* 2010;48:440–4.
- 25 Gursay-Ozdemir Y, Qiu J, Matsuka N, *et al.* Cortical spreading depression activates and upregulates MMP-9. *J Clin Invest* 2004;113:1447–55.
- 26 Martins-Oliveira A, Speciali JG, Dach F, *et al.* Different circulating metalloproteinase profiles in women with migraine with and without aura. *Clin Chim Acta* 2009;408:60–4.
- 27 Li WW, Long GX, Liu DB, *et al.* Cyclooxygenase-2 inhibitor celecoxib suppresses invasion and migration of nasopharyngeal carcinoma cell lines through a decrease in matrix metalloproteinase-2 and -9 activity. *Die Pharmazie* 2014;69:132–7.
- 28 Li WZ, Huo QJ, Wang XY, *et al.* Inhibitive effect of celecoxib on the adhesion and invasion of human tongue squamous carcinoma cells to extracellular matrix via down regulation of MMP-2 expression. *Prostaglandins Other Lipid Mediat* 2010;93:113–19.
- 29 Kim GM, Jin KS, Chung CS. Differential effects of corticosteroids on the expression of cyclooxygenase-2, tumour necrosis factor-alpha and matrix metalloproteinase-9 in an animal model of migraine. *Cephalalgia* 2008;28:1179–87.
- 30 Chen YF, Zhang CY, Zhang XY, *et al.* [Effects of acupuncture combined with medicine on expression of matrix metalloproteinase-2 in the rat of endometriosis]. *Zhongguo Zhen Jiu* 2008;28:675–80.
- 31 Lau WK, Lau YM, Zhang HQ, *et al.* Electroacupuncture versus celecoxib for neuropathic pain in rat SNL model. *Neuroscience* 2010;170:655–61.
- 32 Gerlach RF, Meschiari CA, Marcaccini AM, *et al.* Positive correlations between serum and plasma matrix metalloproteinase (MMP)-2 or MMP-9 levels in disease conditions. *Clin Chem Lab Med* 2009;47:888–91.
- 33 Palei AC, Sandrim VC, Amaral LM, *et al.* Association between matrix metalloproteinase (MMP)-2 polymorphisms and MMP-2 levels in hypertensive disorders of pregnancy. *Exp Mol Pathol* 2012;92:217–21.
- 34 Gomes VA, Vieira CS, Jacob-Ferreira AL, *et al.* Imbalanced circulating matrix metalloproteinases in polycystic ovary syndrome. *Mol Cell Biochem* 2011;353:251–7.