

SHORT REPORT

No relation between cephalic venous dilatation and pain in migraine

Dorthe Daugaard, Lars Lykke Thomsen, Jes Olesen

Abstract

Evidence for the involvement of the cranial arterial system in migraine is plentiful, but it is unclear whether the cranial venous system may be involved in the mechanism of migraine pain. Venules are the preferentially involved vessels in the neurogenic inflammation animal model of migraine. The cranial and cerebral veins and sinuses are pain sensitive and receive sensory innervation from the trigeminal nerve. If the veins are involved in migraine pathogenesis, a venous dilatation would presumably be painful. The effect of a short lasting cranial venous dilatation, induced by applying pressure on the internal jugular veins (Queckenstedt's manoeuvre), was therefore compared with a placebo procedure, consisting of an equal pressure applied on to the lateral aspect of the neck. In each procedure pressure was applied for 10 seconds. The study used a single blind, randomised, cross over design, and 20 patients with an acute attack of migraine without aura participated. After each procedure, headache intensity was rated on a standardised five point scale. After Queckenstedt's manoeuvre 40% of the patients reported no change in headache intensity, 25% a worsening, and 35% an improvement of their headache. No significant difference between the headache intensity ratings during Queckenstedt's manoeuvre and the placebo manoeuvre was found ($p=0.22$). The findings make it unlikely that the cephalic venous system is of major importance in migraine pain mechanisms and, therefore, also less likely that neurogenic inflammation plays a significant part in humans during attacks of migraine without aura.

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The cranial vascular system is most certainly involved in migraine pain, although the relative importance of the different components of the vasculature is not fully determined. The arterial system, according to many authors, is

the most likely principal site of action,¹ but some findings have suggested that the venous system may also contribute.

Migraine pain is mostly described as throbbing or pounding, but it may also be pressing and constant in many patients.² Three widely used and effective antimigraine drugs—dihydroergotamine, ergotamine, and sumatriptan—are vasoconstrictors. All of the three drugs also cause venoconstriction; ergotamine has a very long lasting constrictory effect on the veins, and dihydroergotamine predominantly constricts the veins.^{3,4} The vasodilator nitroglycerin may induce headache and migraine attacks in migraineurs and shows a stronger dilatory effect on veins than on arteries.⁵ Yet another reason to study the importance of the venous system in migraine is the preferential involvement of venules in neurogenic inflammation,⁶ which is the most widely accepted animal model of migraine.⁷

Queckenstedt's manoeuvre induces dilatation of intracranial and extracranial veins, causing stretching of the venous walls and the surrounding perivascular nerves. If the veins and venules were affected by the disease mechanisms of migraine, a venous dilatation would aggravate migraine pain.

The objective of the present study was to compare the effect of a short lasting dilatation of the cranial venous system obtained by the manoeuvre of Queckenstedt to a placebo procedure during an acute attack of migraine without aura.

Methods

SUBJECTS

The study was single blind, randomised, and placebo controlled. Twenty patients participated (mean age 44 years, range 20-61 years, male:female ratio 1:19); all had migraine without aura as defined by the diagnostic criteria of the International Headache Society.⁸ The patients were recruited among participants in trials of new drugs for the treatment of acute migraine attacks. Patients presented with a typical attack of migraine without aura at the headache clinic and the participants fulfilled the criteria set by the trial protocol. All had between one and six migraine attacks a month, and were otherwise healthy. None of the participants received migraine prophylactics or other daily medication. Patients with tension

1365 East Evergreen Drive 2, Palatine, Illinois 60067, USA
D Daugaard

Department of Neurology, Glostrup Hospital, University of Copenhagen, DK-2600 Glostrup, Denmark
L L Thomsen
J Olesen

Dorthe Daugaard, 1365, E. Evergreen Drive #2, Palatine, Illinois 60067, USA.
Telephone 001 847 963 9463; fax 001 847 963 9464; email: dorthe@ix.netcom.com

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Table 1 Clinical characterisation of the headache and the accompanying symptoms

Patients (n)	20
Mean age (y, range)	44 (20–61)
Male:female ratio	1:19
Duration of headache (mean (range))	4 h 48 min (2 h 30 min–9 h 30 min)
Lateralisation of headache	80% unilateral (n=16) 20% bilateral (n=4)
Intensity of headache	70% moderate (n=14) 30% severe (n=6)
Quality of pain	30% throbbing (n=6) 50% pressing (n=10) 20% missing values (n=4)
Worsening by physical activity	95% (n=19)
Nausea	85% (n=17)
Vomiting	25% (n=5)
Photophobia	90% (n=18)
Phonophobia	55% (n=11)

type headache more than once a month were excluded, as were patients who had taken ergotamine, sumatriptan, or weak analgesics in the preceding 48, 24, and 6 hours, respectively.

All patients gave written consent and the study was approved by the ethics committee of Copenhagen County.

PROCEDURE

After 30 minutes of rest in the supine position, the headache was rated as mild, moderate, or severe and the accompanying symptoms were characterised according to the International Headache Society criteria. With the patient in the sitting position and the examiner standing behind the patient, Queckenstedt's manoeuvre and a placebo manoeuvre were performed in random order. Queckenstedt's manoeuvre was performed by applying a constant, equal pressure on both internal jugular veins at the limb of the thyroid cartilage, anteriorly in the neck, for 10 seconds. The placebo manoeuvre was performed by applying an equal pressure on to both sternomastoid muscles at the lateral aspect of the neck. After each manoeuvre, the participants were asked: "Is your migraine headache unchanged, worse, much worse, better, or much better right now?" After stating their reply, the pressure was released. All participants were examined by the same investigator.

STATISTICS

Randomisation was done using MEDSTAT. The data were analysed using a marginal homogeneity test (StatXact, version 2), performed by the Department of Biostatistics at the University of Copenhagen.

Results

Table 1 shows the characteristics of the studied attacks.

Table 2 The effect of Queckenstedt/placebo on headache intensity

	Queckenstedt				
	Much worse	Worse	Unchanged	Better	Much better
Placebo					
Much worse					
Worse		2			
Unchanged		2	5	3	
Better		1	2	3	
Much better			1	1	
			n=20, p=0.22		

During Queckenstedt's manoeuvre eight out of 20 patients reported unchanged headache intensity compared with baseline rating, five out of 20 reported a worsening, and seven out of 20 an improvement of their headache. Ten out of 20 patients had unchanged intensity during placebo, two reported a worsening, and eight patients reported an improvement of headache intensity compared with baseline. Seven patients reported a lower headache intensity during the placebo procedure compared to that during Queckenstedt's manoeuvre, three patients a lower intensity during Queckenstedt's manoeuvre compared with placebo, whereas 10 patients rated the intensity the same during both procedures.

No significant difference in headache intensity was found between the manoeuvre of Queckenstedt and the placebo manoeuvre ($p=0.22$, marginal homogeneity test) (table 2).

Discussion

The aim of the present study was to evaluate the effect of venous dilatation on migraine pain. Queckenstedt's manoeuvre increases the pressure in the extracranial and intracranial veins and sinuses and increases the intracranial pressure, the latter being the reason for the long known clinical value of the test. We chose Queckenstedt's manoeuvre rather than Valsalva's manoeuvre, to achieve a more constant and equal venous dilatation in all patients, without simultaneous cardiovascular changes. Valsalva's manoeuvre causes marked changes in heart rate and blood pressure and also causes straining of respiratory and possibly pericranial muscles. Pure breath holding would not cause a sufficient dilatation. The pressure applied on to the upper portion of the sternomastoid muscles (placebo) did not affect the veins due to the underlying transverse processes of the cervical vertebrae.

An effort was made to objectively describe whether a sufficient applied pressure was performed during Queckenstedt's manoeuvre. In colleagues without headache, reddening of the facial skin and protruding facial vessels were evident and a pounding feeling in the head related to heartbeat was reported. However, in patients with migraine, these changes were inconsistent, while some already felt a throbbing pain in the head and were flushing. Bentsen *et al* reported a small within observer and a larger between observer variation in palpation of muscles of the head and neck.⁹ To reduce variability we therefore used the same investigator throughout the study. The intracranial pressure or venous pressure was not measured and it has been reported that the intracranial pressure may vary between patients during Queckenstedt's manoeuvre.¹⁰

Although the characteristics of the studied migraine attacks were similar in characteristics to attacks found in a population based study, there were small differences.² Thus the frequency of photophobia, nausea, and worsening by physical activity were almost identical, whereas vomiting was less frequent in the present study. The intensity of pain was lower and less patients had throbbing headache

compared with the population based, epidemiological study. The explanation for the differences is probably that clinical characterisation of the migraine attacks in the present study described only a short moment of a single attack, and that the patients were lying down in a quiet, dark laboratory.

The results show no significant difference between Queckenstedt's manoeuvre and placebo. Thus the obtained venous dilatation did not aggravate migraine pain.

Neurogenic inflammation can be elicited in animals by electrical stimulation of sensory nerves and ganglia. This causes plasma extravasation and vasodilatation, and this has been shown in rat *dura mater*.⁶ This phenomenon can be blocked by sumatriptan and ergotamine.¹¹ Neurogenic inflammation is currently the most widely used and accepted experimental animal model of migraine. In this model, the most conspicuous changes occur around the venules, which show morphological changes; The surface of the endothelium shows irregular elevations and there are numerous endothelial vesicles and cytoplasmic microvillous projections, the second containing pinocytotic vesicles—all of which reflect an increased transendothelial transport. It has been suggested that liberation of potent vasodilators from surrounding perivascular nerves, such as substance P, may initiate the described permeability changes seen in neurogenic inflammation. The perivascular sensory nerves surrounding the intracranial veins are mainly of trigeminal origin and seem to react to vascular distention with increased firing. Thus Kaube *et al* found that mechanical distention of the superior sagittal sinus (in cats) caused activation of the trigeminovascular system.¹²

We found no effect of the increase in venous pressure on headache intensity after the Queckenstedt's manoeuvre. Our study, therefore, does not indicate an important role for the cranial venous system in migraine pain. As the venules are predominantly involved in neurogenic inflammation our results also suggest that neurogenic inflammation is not present or is not of major importance during migraine attacks. Recently, other clinical studies contradicting the neurogenic inflammation model have become available. A direct study of gadolinium enhancement around dural and brain

blood vessels using MRI during attacks of migraine without aura, showed no evidence of extravasation.¹³ In addition, the endothelin receptor antagonist bosentan and the substance P antagonist RPR100893–201 both block neurogenic inflammation, but have shown no effect in aborting migraine attacks in humans.^{14 15}

In conclusion, our study argues against a major involvement of the cranial venous system in the pain mechanisms of migraine and does not support the importance and presence of neurogenic inflammation in migraine.

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