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Content

Chapter 1

Introduction & Scope of this thesis

Introduction

Cluster headache

Cluster headache (CH) is one of the trigeminal autonomic cephalalgias (TACs), a group of primary headaches which share prominent cranial parasympathetic autonomic features. CH is diagnosed by applying its definition of the International Classification of Headache Disorders (ICHD-3 beta).[1] CH attacks most often are very severe, unilateral and (usually) in the distribution of the first branch of the trigeminal nerve. The attacks are accompanied by ipsilateral cranial parasympathetic autonomic features, an ipsilateral partial Horner's syndrome, a sensation of auricular fullness and/or a sense of restlessness or agitation. Untreated attacks usually last for 15-180 minutes (min) and occur from one every other day to eight per day during the episodes when the disorder is active. Headache attacks either occur in one series/cluster period of less than 1 year, or in at least two series/cluster periods of 7 days to 1 year separated by a headache-free period of at least 1 month (*i.e.* Episodic cluster headache (ECH)), or in one series/cluster period of more than 1 year or in at least two series/cluster periods separated by a headache-free period of less than 1 month (*i.e.* Chronic cluster headache (CCH)). CH can be primary or secondary when it occurs for the first time closely related to another disorder which causes headache.[1]

ECH and CCH are reported in at least 80% and 4 to 20% of CH patients, respectively. In the long term, more than 50% of patients will keep the subtype that is present at the time of diagnosis. The lifetime prevalence of CH is 124 per 100,000 and the 1-year prevalence is 53 per 100,000 in population-based studies. 1-Person year incidence ranges from 2.07 (in 1989-1990) to 9.8 per 100,000 (in 1979-1981). A male to female ratio of 4.3:1 has been reported. The mean age of onset is between 29.6 and 35.7 years. CH has a considerable impact on daily living in three quarters of patients,[2] reflected in the name 'suicide headache'. Active suicidal ideation indeed was found in 5.9% in CCH and 6.3% in ECH patients, and even 55% of CH patients have suicidal thoughts during lifetime.[3] Obviously, the enormous impact of CH makes the search for effective treatments of utmost importance. In this search, understanding CH pathophysiology can provide a basis. And in the other way, effective treatments can expand the knowledge of CH pathophysiology.

Cluster headache pathophysiology

Although headaches that we recognise as and mention CH today have been described since the 17th century,[4] extensive study of the pathophysiology and successful treatment had to wait until the second half of the 20th century. In the causation of CH, a centrally driven change in cranial blood vessel diameter is considered to play a role. Pain afferents from the trigeminovascular system traverse the ophthalmic nerve and synapse in the trigeminocervical complex. The second-order neurons project to the thalamus and thalamocortical projections lead to pain awareness. Trigeminal-autonomic reflex

activation of the efferent parasympathetic fibres arising in the superior salivatory nucleus of the facial nerve causes (further) blood vessel dilatation. Dilatation of the carotid artery can result in a third-order sympathetic nerve lesion with a partial Horner's syndrome. Parasympathetic activation also leads to conjunctival injection, lacrimation, rhinorrhoea and nasal congestion.[5] Parasympathetic outflow is also directly activated by the hypothalamus. Moreover, the posterior hypothalamic grey matter region triggers the pain and controls the (typical) circadian rhythm.[6]

Oxygen treatment in the past 60 years and its position

CH treatment comprises of acute/attack treatment and short-term and long-term preventive/ prophylactic treatment. While preventive treatment (not further discussed here) is aimed to reduce the frequency and intensity of CH attacks, the goal of acute treatment is to abort a CH attack within a few min. Nowadays, this can be achieved in most patients by injecting 6 mg of Sumatriptan subcutaneously or inhaling 100% oxygen. Nasal Sumatriptan, nasal(/oral) Zolmitriptan, nasal Lidocaïne, oral/rectal Ergotamine tartrate and nasal/intravenous(/intramuscular) Dihydroergotamine are alternative, but inferior acute treatments, due to a slower effect, unfavourable pharmacologic profile or impractical route of administration.[7]

Oxygen was actually one of the first successful options for acute treatment. In his 1956 publication on 'Histaminic cephalgia', Bayard T. Horton, a CH investigator of the first hour,[8] stated that breathing of 100% oxygen can alleviate an attack considerably when the attack is mild and oxygen is used immediately.[9] Stimulated by a letter to the editor on this topic by Janks,[10] Kudrow took an interest in oxygen treatment for CH and conducted a trial in 1981, which was positive.[11] Today, inhalation of 100% oxygen via a non-rebreathing mask at a flow rate of at least 7 litre/minute (L/min) is still recommended as an acute treatment,[6] although 12 L/min has also been proven to be effective.[12] However, not all patients are able to use oxygen effectively, and it is this ineffectiveness which necessitates further research into pathophysiology and treatment effects, in order to find a treatment regime which is 100% effective (and has negotiable side effects). Here, I will first present a brief overview of the known degrees and modes of effectiveness of inhalation of 100% oxygen at different flow rates and pressures.

Oxygen response rates at flow rates of 6-8 L/min

A number of studies have investigated the acute treatment success achieved by inhalation of 100% pure oxygen at normal (*i.e.* approximately 7 L/min) flow rates.

In the first part of Kudrow's study fifty-two CH patients were treated with 100% oxygen via a facial mask at a flow rate of 7 L/min for 15 min, starting at the onset of each of ten CH attacks. Prophylactic medication was not withheld in twenty-eight patients. 'Treatment success' was defined as 'complete or almost complete cessation of head pain within 15 min for at least seven of ten attacks'. Seventy-five percent of patients successfully treated their CH attacks. In the second part of the study (a

crossover trial), the effectiveness of oxygen inhalation was compared to that of sublingual ergotamine tartrate administration. An additional fifty patients were treated with 100% oxygen via a facial mask at a flow rate of 7 L/min for 15 min starting at the onset of each of ten CH attacks, and sublingual ergotamine tartrate or *vice versa*. Prophylactic medication was withheld. Eighty-two percent of the oxygen users successfully treated their CH attacks.[11]

In Fogan's double-blind crossover study, treatments of 100% oxygen and compressed room air, both supplied via a non-rebreathing face mask at a flow rate of 6 L/min for up to 15 min, were compared. Nineteen CH patients were treated with each treatment/gas for zero to nine (oxygen) or ten (air) CH attacks. 'CH pain relief' was scored '0 for no relief, 1 for slight relief, 2 for substantial relief and 3 for complete relief'. The 'relief score' was an average of the scores. The average relief score with oxygen was 1.93 and with air was 0.77. The difference between the average relief scores was statistically significant ($p < 0.01$). As a continuation of the Kudrow study, this study ruled out the possible effects of pressurised gas flow itself, the breathing mask and the attention on the person's own breathing.[13]

In Heckl's study, ten patients (eight with CH and two with Chronic paroxysmal hemicrania (CPH)) were treated with oxygen via an oxygen mask at a flow rate of 7 L/min at the onset of a headache attack. All six ECH patients already experienced relief at treatment onset. Mean pain reduction was 60-80%. A primary chronic cluster headache (PCCH) patient had only a temporary mean pain reduction of 60%, with a reduction in attack duration of 67% to circa 20 min. A secondary chronic cluster headache (SCCH) patient had a pain reduction of most 60-70%, without a reduction in attack duration.[14]

In a study conducted by Gallagher *et al.* abortive treatments of analgesics (most commonly 'combination-type medications containing barbiturates or narcotics') and/or 100% oxygen (supplied via a face mask at a flow rate of 8 L/min for 10-15 min) were compared. All sixty patients were offered both treatments. 'Significant (headache) relief' (no definition given) was reported in thirty-nine of fifty-one (*i.e.* 76%) patients, who first chose oxygen inhalation therapy compared to ten of forty-eight (*i.e.* 21%) patients, who first chose analgesics. However, only 31% of patients preferred to continue using oxygen inhalation, compared to 65% of patients who chose to continue using analgesics. The efficacy of oxygen treatment did not outweigh the unpractical use and the occurrence of rebound CH.[15]

Higher oxygen flow rates of 12-15 L/min

Seven L/min has become the standard and minimal oxygen flow rate since Kudrow's study.[11] When I started my studies on CH and oxygen in 2008, there was only one small study with only three CH patients, who were resistant to standard oxygen flow rates of 7-10 L/min, and who inhaled oxygen at flow rates of 14-15 L/min. 'Alleviation', '70-100% relief' and 'full headache relief' were achieved

multiple times using these higher oxygen flow rates. The author suggested that flow rates up to 15 L/min should have been used before CH patients are considered unresponsive to oxygen treatment.[16]

More recently, a trial was published with high flow oxygen, in which 12 L/min was found to be an effective treatment. In Cohen's double-blind crossover trial 100% oxygen and air, both supplied via a non-rebreathing face mask at a flow rate of 12 L/min for 15 min, were compared. Of the seventy-six ECH and CCH patients who completed the study, seventy-three CH patients treated two CH attacks each with each treatment/gas and were included in the primary analysis. A pain free state (or a state of 'adequate relief' (not defined)) after 15 min of inhalation was achieved in 116 out of 150 (*i.e.* 78%) oxygen-treated and 29 out of 148 (*i.e.* 20%) air-treated CH attacks. The difference was statistically significant ($p < 0.001$).[12]

Mechanisms of action of normobaric oxygen

The mechanisms underlying the antinociceptive effect of oxygen are not well understood. Initially a primary vascular target was presumed. Sakai *et al.* suggested at first that inhalation of 100% oxygen during a CH attack reduces the cephalic flow and thereby relieves pain. The *in vitro* evidence for oxygen directly causing vasoconstriction of cerebral blood vessels was discussed.[17] Further endorsement of a direct or indirect vasoconstrictor effect of 100% oxygen came from a reduction in pulsation amplitude of (terminal) branches of the internal and external carotid vasculature, particularly on the symptomatic side, during 10 min of breathing of 100% oxygen in nitroglycerin-induced CH attacks.[18] Moreover, other studies, applying Xenon, visualised a reduction in cerebral blood flow due to oxygen inhalation in spontaneous[19, 20, 21] and nitroglycerin- or alcohol-induced CH attacks.[21] During the conduction phase of our studies on CH and oxygen evidence was published on an indirect vasoconstrictive effect of 100% oxygen, which inhibited a subpopulation of efferent neurons projecting from the superior salivatory nucleus (*i.e.* the aforementioned origin of neurons for the cranial parasympathetic vasodilator pathway), by maximally 33% at 20 min.[22]

Most pain reduction, simultaneously with a reduction in autonomic symptoms, was found in patients with an abnormally high reduction of cerebral blood flow induced by oxygen inhalation during CH attacks. However, some pain relief was also found in patients with a normal cerebral blood flow response, suggesting other factors than vasoconstriction causing pain relief as well as a relation between pain intensity and autonomic symptoms.[19] Schuh-Hofer *et al.* demonstrated that hyperoxia significantly inhibited rat dural protein plasma extravasation and therefore counteracted neurogenic inflammation.[23]

Factors determining normobaric oxygen response

At the start of my research, I specifically assumed that factors determining oxygen response could contribute to our knowledge of CH pathophysiology. At that time, it was not known which characteristics predicted acute treatment response in CH patients completely. Table 1 shows the

factors that had been associated with an unfavourable response to oxygen. Schürks *et al.* identified restlessness (OR 0.09, $p = 0.019$) as a negative predictor of oxygen response. It was hypothesized that restlessness causes intolerance of the oxygen face mask in some.[24] Restlessness during a CH attack was reported by 67.9% of patients.[25]

Kudrow found significantly better ($p < 0.05$) effects of oxygen inhalation in ECH patients under 50 years of age ('treatment success' 92.9%) than in CCH patients over 49 years of age ('treatment success' 57.1%). There was no significant response difference between 'young' (*i.e.* under 50 years of age) and 'old' (*i.e.* over 49 years of age) CH patients. Neither was there a significant response difference between ECH and CCH patients in all age groups.[11] Likewise, Schürks *et al.* did not identify age and ECH (%) as statistically significant negative predictors of oxygen response.[24]

Kudrow and Schürks *et al.* both found no significant response difference between male and female patients.[11, 24, 25] However, Rozen *et al.* found an oxygen treatment response in only 59.1% of women, versus 87% of men. This difference was significant ($p = 0.01$).[26]

In another study, Rozen noted that a history of smoking was reported by 75% of women, versus 61% of men.[16] Schürks *et al.* did not identify current smoking (%) as a statistically significant negative predictor of oxygen response.[24] There were statistically significantly more male current smokers than female current smokers.[25]

Rozen *et al.* found significantly more vomiting (46.9% *versus* 17.4%, $p = 0.003$) and more nausea (62.5% *versus* 43.5%, $p = 0.09$) in women.[26] Schürks *et al.* identified nausea/vomiting as a negative predictor of oxygen response (OR 0.41, $p = 0.029$).[24] Nausea and vomiting were reported by 27.8% during CH attacks.[25]

Kudrow noted that in some cases, unresponsive to either oxygen or ergotamine, the acute CH attack treatment had been started late.[11] Schürks *et al.* stated it was less obvious whether the timing of acute treatment influences treatment success, because no data were available to further underpin this issue.[24]

Table 1. Factors associated with an unfavourable response to oxygen in CH attacks

Factors	*p* value
Restlessness [24]	0.019 [a]
CCH and > 49 years of age [11]	< 0.05 [b]
Females [11, 24, 25, 26]	0.01 [c] – 'no significance' [c]
Nausea and vomiting [24, 26]	0.029 [a]

[a] Oxygen responders (defined by the criterion: 'compared to untreated CH attacks, CH pain must have been reduced in at least three CH attacks by at least 50% within 15 min after oxygen application and despite the used flow rate') were compared to non-responders (who should have used therapeutic flow rates).[24]

[b] ECH patients < 50 years of age were compared to CCH patients > 49 years of age.[11]

[c] Females were compared to males.[25, 26]

Hyperbaric oxygen

The rather successful use of oxygen led to experiments with hyperbaric oxygen (HBO). Porta *et al.* stated that a high blood oxygen saturation of 98% during min is required for treatment success, which can be induced by HBO inhalation. After the initial case report by Weiss, Porta *et al.* first confirmed that HBO inhalation could be effective for individual CH attacks.[27] HBO consists of 100% oxygen at a pressure more than 1 atmosphere. Two studies investigated the acute treatment effect achieved by inhalation of HBO.

In the crossover study conducted by Porta *et al.*, abortive treatments of 'normobaric oxygen inhalation' (at a flow rate of 7 L/min for 15 min) and HBO inhalation (administered in a hyperbaric chamber with 100% oxygen with compression up to 2 atmosphere absolute (ATA)) were compared. In contrast to five patients who were 'partially refractory' and three patients who were 'totally refractory' to normobaric oxygen inhalation, all fourteen patients achieved 'complete relief' a few min after starting HBO treatment.[27]

A double-blind study by Di Sabato *et al.* compared the acute treatment effect of HBO (administered in a hyperbaric chamber during 30 min with a pressure up to 2.5 ATA, in seven ECH patients) and of a placebo procedure (normal air administered in a hyperbaric chamber during 30 min at a pressure of 1.0 ATA, in six ECH patients) both to the mean of the duration of the last three CH attacks occurring before the test. HBO interrupted the CH attack in 86% of patients, whereas placebo did not change the duration of CH attacks in 100% of patients (so one can expect there was no interruption).[28] However, the difference was not statistically significant ($p = 0.08$).[29]

As expected, Di Sabato *et al.* realised that HBO as an acute treatment is not practical, because of the short duration of CH attacks and the costs of HBO treatment.[28] Pascual *et al.* suggested that HBO

could have prophylactic effects.[30] Five studies investigated the prophylactic treatment effect achieved by inhalation of HBO.

In the study by Di Sabato *et al.* described above, of the six patients (*i.e.* 86%) in which HBO interrupted the current CH attack, three patients did not have CH attacks for 4-6 days and another three patients did not have CH attacks during the follow-up period of 2 months. The CH attack pattern remained unchanged in the patients on placebo.[28]

Pascual *et al.* studied the frequency and duration of CH attacks during HBO treatment (ten sessions administered in a hyperbaric chamber for 70 min per session at a pressure of 2.5 ATA), compared to the last (minimum) 2 weeks before treatment start. The four CCH patients continued using preventive treatment (Lithium). One patient did not have any CH attacks until 31 days after his 8 day treatment. In contrast, another patient did not experience any effect in frequency (and duration).[30]

Nilsson Remahl *et al.* conducted a double-blind crossover study in which HBO treatment (composed of 100% oxygen) and hyperbaric normoxic placebo treatment (composed of 10% oxygen), both supplied in a hyperbaric chamber by a mask for 70 min in two sessions 24 hours apart at 2.5 ATA, were compared. Fourteen CH patients breathed HBO, sixteen CH patients breathed hyperbaric normoxic placebo. 'A headache index' (HI) (sum of (number of headache attacks times their degree of severity)) was calculated for 1 week prior to as well as for 1 week following each separate treatment. A treatment was considered effective if the HI decreased by > 50%. HBO treatment was effective in five of fourteen (*i.e.* 36%) patients and hyperbaric normoxic placebo treatment was effective in six of sixteen (*i.e.* 38%) patients.[31] There was no significant ($p = 0.92$) difference in treatment effectiveness between HBO and hyperbaric normoxic placebo treatment.[29] One ECH patient who responded to HBO was free of CH attacks for 6.5 months. However, two ECH patients who responded to hyperbaric normoxic placebo treatment had a remission period (free of CH attacks) for even more than 1 year. The study only found a true preventing effect of (100%) oxygen while the patient was under hyperbaric conditions.[31]

Di Sabato *et al.* placed seven ECH patients in a hyperbaric chamber during 30 min with pressures up to 2.5 ATA. A disappearance or at least a 50% diminution 'of the CH' (unknown frequency, duration or severity) was observed during 3 days after exposure.[32] In another study by Di Sabato *et al.* ten CCH patients were placed in a hyperbaric chamber during fiteen sessions of 30 min with pressure up to 2.5 'atm abs' while breathing 100% oxygen administered through a facial mask. There was a decrease in the weekly number of attacks during the treatment period (*i.e.* 30 days). The 'clinical index' (not defined) remained at 'significantly' lowered numbers during the first 2 weeks of a 4-week follow-up period after HBO treatment.[33]

The authors mentioned several mechanisms that could explain the effect of HBO. It induces vasoconstriction, reduces cerebral hypoxia by increasing oxygen diffusion, acts against oedema of the blood vessel wall and *interstitium* and stimulates the serotonin synthesis in the central nervous system.[28] *In vitro* a normal 5-Hydroxytryptamine (5-HT) turnover was found after HBO.[33]

Furthermore, HBO could act against the sterile inflammation produced by release of neuropeptides from the trigeminal neuron.[32] Finally, HBO has some nonspecific actions such as an influence in the prostaglandin cascade.[30]

Cold air

Mc Leod *et al.* investigated the interesting hypothesis that cooling rather than the oxygen concentration plays the main role in relieving a CH attack as cold temperature causes vasoconstriction. Eight CH patients treated ten CH attacks using a device which delivered room air cooled to 5°C via a non-rebreathing face mask at a flow rate of 6 L/min for 15 min or until the headache was aborted. Of these eight CH patients, six treated the next five CH attacks using 100% oxygen (no details of administration were provided). The level of relief was scored '0 for no or minimal relief, 1 for slight relief, 2 for substantial relief and 3 for complete relief'. 'Significant relief' combined categories 2 and 3. 'Significant relief' was achieved in 85% ($p < 0.0005$) using the cold room air device and in 83% ($p < 0.0005$) using 100% oxygen. The main relief score for the sixty-eight observations in which cold room air provided 'significant relief' was 2.69 and for the twenty-five observations in which 100% oxygen provided 'significant relief' was 2.72. The difference between the main relief scores was not statistically significant. So, contrary to Fogan's and Cohen's results, cold room air can be effective in the acute treatment of CH.[34]

To summarize, 100% oxygen supplied via a facial mask at a flow rate of 7 L/min given at pain onset for 15 min, provides successful headache relief in 75-82%. Patients who have no response to 100% oxygen at a flow rate of 7 L/min should be exposed to flow rates of 12 and possibly even 14-15 L/min, before they are considered refractory. Restlessness, an age > 49 years in CCH, (female gender) and nausea and vomiting are proven factors predicting a negative oxygen response.

HBO of 2.0–2.5 ATA can terminate CH attacks in a few to 30 min in 86% to probably 100%. HBO can terminate CH attacks also in those considered refractory to normobaric oxygen. HBO cannot prevent subsequent CH attacks.

Cold (5°C) room air supplied via a face mask at a flow rate of 6 L/min for 15 min was as effective in relieving pain as 100% oxygen.

Scope of this thesis

When I started my studies in 2008, it was not possible to find clues that provided further insight into CH pathophysiology, based upon the data on proven factors predicting the oxygen response in CH attacks in particular. It led me to believe that it would be worthwhile to set up a systematic search for characteristics that would predict the effect of oxygen in CH.

I referred shortly to the history of oxygen application for CH in the past 60 years. As is true for the rebound phenomenon, which had been noted by Kudrow in 1981 already,[11] I increasingly realised more things could be learned from the past. Being interested in the origin of applying oxygen for CH, which provides a perspective for our studies, I did a more extensive historical review of CH and oxygen therapy (chapter 2).

I carried out a retrospective (chapter 3) and subsequently a prospective (chapter 4) cross-sectional correlation study. Although described in more detail in the prospective study, in both studies I used the same classification in five groups of response to oxygen, which enabled a comparison.

In my retrospective study, six patients spontaneously reported an increase in CH attack frequency when using oxygen as acute treatment. Because this phenomenon implies an important limitation in the use of oxygen, in my prospective study I specifically asked for a change in CH attack frequency after start of oxygen therapy. During the course of my prospective study, 7% of the patients reported the phenomenon. As Kudrow described a rebound phenomenon in even 25% of his patients using oxygen for CH,[11] I decided not to wait until the final patient inclusion in my prospective study, and I studied the phenomenon more closely in my patient series present at that time. To study the rebound phenomenon, first I had to define it. This definition and the results of the study will be presented in chapter 5.

Apart from studying clinical characteristics, during the course of our studies I became interested in clinical neurophysiology as a means for further elucidation of pathophysiological mechanisms in CH. To investigate the (direct or indirect) effect of oxygen on medullary interneurons, I intended to study the nociception specific blink reflex before and during a CH attack, as well as before and during oxygen treatment. This study had unexpected, serendipitous results, that are described in chapter 6. As the remaining data from this study, notably the effect of oxygen on the nociception specific blink reflex may be useful in further research, I described these data in an additional chapter 7.

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Chapter 2

The history of oxygen inhalation as a treatment for cluster headache

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Abstract

Overview. Oxygen has been a generally accepted treatment method for cluster headache attacks ever since Kudrow (1981) conducted a controlled trial showing that oxygen was equally or even more effective than ergotamine injections.

Purpose. The aim of the present study was to provide a historical perspective of oxygen treatment in cluster headache and to find the origin of this treatment. Oxygen for cluster headache was first described by Horton in 1952 and for migraine patients in 1940 by Alvarez. At the time, neither of the authors provided any reason why they chose for this treatment method. The vasoconstrictive effect of oxygen was not described by Horton until 1961.

Conclusion. We suggest that these authors originally adhered to the vasoconstrictive theory of vascular headache that was prevalent in the early 20th century until Wolff demonstrated the contrary in the late 1930s. The early literature describes an analogy between angina pectoris and migraine, as being both due to vasoconstriction. As oxygen was described as a treatment for angina pectoris, this may be the reason why oxygen was tried for migraine and cluster headache at a time when they were not recognized as separate entities. Later on it turned out to be more effective for cluster headache.

Introduction

Oxygen has been used to treat cluster headache (CH) attacks since Horton first described it in 1952.[1] The mechanism by which oxygen relieves CH attacks is still unclear, as is the pathophysiology of CH itself. In this article we will provide a historical perspective of oxygen treatment in CH and figure out why we started treating our CH patients with oxygen in the first place.

History of cluster headache

One of the earliest descriptions of a 'cluster headache-like syndrome' dates back to the 17th century.[2] The Dutch physician Nicolaes Tulp (1593-1674) described the headache history of a Dutch man, which seemed to fit a diagnosis of CH, although autonomic symptoms were hardly described. Several cases describing symptoms that nowadays would be recognized as CH have been published since then.[3, 4, 5]

In 1926 the London neurologist Wilfred Harris (1869-1960) gave the first complete description of CH, which he named migrainous neuralgia or ciliary (migrainous) neuralgia (if the symptoms were mostly located near the eye).[6] He noticed a clear difference in clinical characteristics between migrainous neuralgia, migraine and trigeminal neuralgia. He described the unilaterality, frequency and autonomic features that we now know are typical for CH. He also recognized that Horner's syndrome could occur and he described the so-called 'cluster phenomenon'.[7] Harris treated his patients with alcohol injections, at first in or around the supraorbital and infraorbital nerve and later in the Gasserian ganglion.[8] Later, he noticed the positive effect of subcutaneous injections of ergotamine that had become available previously.[9]

In 1939, Bayard Horton (1895-1980) described cluster attack features and a specific treatment method using histamine desensitization in a paper called 'A new syndrome of vascular headache: results of treatment with histamine'.[10] The association with histamine was possibly related to one of the current pathogenic allergy theories, in which migraine was compared to asthma and urticaria. Horton speculated that CH was caused by an 'anaphylactoid reaction' to endogenous histamine.[11, 12] He was probably not aware that Harris in 1926 already described the syndrome we now know as CH.

Only in 1952 did Horton detail the pain and its associated symptoms, and the syndrome then became well known.[1] Twelve years before the publication of his 1939 article, he had noticed patients with erythromelalgia of the feet. He noticed the extreme grades of vasodilatation that were associated with their complaints of burning distress. In CH patients he noticed an increase in surface temperature of the painful areas, roughly corresponding to the branches of the external carotid artery. Hence the term 'erythromelalgia of the head' was proposed. Later, he noticed the effect of histamine in provoking an attack and as he thought that there was an important pathogenic role for the vasodilator histamine, he called the disease 'histaminic cephalgia'.

The term ‘cluster headache’ was introduced by Kunkle *et al.* in 1952, but ‘Horton’s headache’ and ‘histaminic cephalgia’ were more frequently used names at first.[13] Horton treated his patients with oxygen and ergot preparations but mostly by histamine desensitization.

In 1961, Horton referred to one of his earlier unpublished papers (1938) entitled: ‘Migraine: treatment with histamine’.[14] This paper was published under the name ‘A new syndrome of vascular headache: results of treatment with histamine’ in 1939 and turned out to be his first discussion of CH.[10] This shows that migraine and CH were considered similar clinical entities of vascular origin before the clinical descriptions of Horton himself and Harris became known.

Horton and oxygen treatment

Nowadays oxygen is frequently used as an acute treatment for CH attacks.[15, 16] As mentioned above, it is still not clear why oxygen aborts CH attacks so well. Recent studies show that activation of the trigeminovascular system, along with the autonomic reflex arc, are important in the pathophysiology of CH.[17] Akerman showed that treatment with 100% oxygen in rats was able to inhibit neuronal firing in the trigeminal cervical complex and to attenuate the blood flow changes in response to stimulation of the facial/greater superficial petrosal nerve efferents. Oxygen treatment had no effect on activation of trigeminal afferents in response to stimulation of dural structures. It seems that oxygen acts on the parasympathetic pathways to exert its abortive effects, rather than directly on trigeminal afferents to the dural vasculature.[18] More study on the subject is still required to gain more insight into the pathophysiology and potential treatment methods of CH.

What is the origin of the use of oxygen as a treatment for CH? Working at the Mayo clinic (Rochester, Minnesota, USA) in 1940, Alvarez described his usage of oxygen in the treatment of headache.[19] He used a nasal mask to deliver oxygen at a flow rate between 6 and 8 litre/minute (L/min). He believed that it was effective for the treatment of typical migraine, and that it gave some relief in a group of patients he called ‘Probably not migraine or else migraine with complications’ and in a group called ‘Headache, not migrainous’. In the ‘Typical migraine’ group, 88% of the patients noticed relief to some extent, 42% had complete relief and 36% much relief. In the ‘Probably not migraine or else migraine with complications’ group only 33% and in the ‘Headache, not migrainous’ group only 40% noticed any relief. Histaminic cephalgia, or any other description of CH, was not yet mentioned separately, but it seems likely that CH patients may have been included in the ‘Typical migraine’ and ‘Probably not migraine’ groups.

The first time that oxygen therapy was recommended as a possible treatment method for CH attacks was in Horton’s 1952 paper.[1] In 1955, in the *Bulletin of the Tufts,* Horton described the successful treatment with oxygen in a population of 1176 patients with histaminic cephalgia.[20] However, this was not a systematic study, as it was solely based on his experience in the clinic. He usually recommended oxygen usage in combination with an intravenous injection of dihydroergotamine. Oxygen without dihydroergotamine was found effective in less severe CH attacks,

which he graded 1 and 2, but of little value in severe attacks, graded 3 and 4. Furthermore, he noticed that oxygen was most effective when the oxygen treatment was started promptly at the onset of an attack. The reason why Horton started using oxygen as a treatment is not clear from his early papers. He may have followed up on Alvarez, who treated migraine with oxygen, not describing why he did so either. However, Horton stated that the pain in episodes of histaminic cephalgia was caused by vasodilatation of extracranial vessels and he noted that the intravenous administration of 1:500,000 solution of epinephrine could also be used to abort attacks. He also noted that epinephrine constricts the extracranial vessels, which may have been a clue for his ideas on the pathophysiological origin of CH. Whether he was really aware of the vasoconstrictive effects of oxygen, and whether this is why he tried to use oxygen in his clinic in the first place, is not clear. Of course, it is also possible that the effective use of oxygen was discovered by coincidence.

If we assume that the vasoconstrictive effect of oxygen was known, it would seem reasonable to treat both migraine and CH with oxygen, as Horton at first described them as variations of the same disease. In his 1959 paper 'Management of vascular headache', Horton made a distinction between migraine and histaminic cephalgia.[21] In migraine he distinguished three phases but in histaminic cephalgia only two. In migraine, the first phase was supposed to be due to vasoconstriction, not giving rise to pain but rather to scotomata and other cortical manifestations. This phase does not occur in histaminic cephalgia. The vasodilating second phase was thought to explain the associated pain. It would occur more promptly in histaminic cephalgia than in migraine. The third phase was thought to be due to oedema, which was also believed to cause pain. This is short lasting in histaminic cephalgia but may persist for hours in cases of migraine, explaining the difference in symptom duration (Table 1).

In this paper,[21] Horton also described the treatment of both migraine and histaminic cephalgia. He mentioned the effectiveness of vasoconstricting agents in migraine. Oxygen, however, was not listed among them. In the same article, oxygen was mentioned as an acute treatment for histaminic cephalgia, but again without any reasoning why this was done. Not until 1961 in the *Maryland State Medical Journal* was oxygen described by Horton as a vasoconstricting agent.[14] In that article, he also referred to treating other vascular headaches with oxygen, without mentioning the results of this treatment.

In conclusion, we can say that there is no clear documentation of why Horton started using oxygen therapy as an acute treatment for CH patients and why Alvarez used it in all headache patients. In the following section we will try to formulate why they may have done so.

Table 1. Pathophysiologic mechanism for 'histaminic cephalgia' and migraine according to Horton (1959) [21]

	Vasoconstriction	Vasodilatation	Oedema
Migraine	+	+	+ (long lasting)
Histaminic cephalgia	-	+	+ (short lasting)
Associated symptom	Cortical symptoms (e.g. scotomas)	Pain	Pain

The use of oxygen before Horton

There was a period in which sympathicotonic (with pale face) as well as sympathicolytic (with red face) types of migraine were distinguished in textbooks. This resulted from the discussion in the 1850s and 1860s following the discovery of the vasomotor nerves,[22] although the angiospastic concept of migraine was discussed earlier (e.g. by Parry [23]). These ideas on the pathophysiological mechanisms underlying migraine (sympathicotonic and sympathicolytic) existed next to each other for several decades, although Latham tried to combine these ideas, suggesting vasoconstriction in the aura phase followed by vasodilatation in the headache phase (1873).[24] On one side there was Edward Woakes, who introduced ergot for its vasoconstrictive effect in the treatment of migraine (1868),[25] and on the other side there was a period in the early 20th century in which ergotamine was thought to block the sympathetic nerve effects and was therefore used as the treatment for sympathicotonic conditions, including migraine. It would appear later that this was a matter of dosage, lower dosages being vasoconstrictive (as in the case of Woakes) instead of vasodilatating (in the early 20th century applications).[26] In his 1935 review of migraine in Bumke's and Foerster's *Handbuch der Neurologie*, Hugo Richter (1886-1945) stated that from all evidence available at that time, the vasoconstrictive model of migraine was the most plausible.[27]

In the 1930s, John Graham and Harold Wolff studied the external carotid arteries by measuring the amplitude of pulsations following ergotamine injections, which showed a simultaneous decrease in amplitude and decline in migrainous headache. A relationship with cerebrospinal fluid pulsations (reflecting intracranial artery extension) was not observed. They concluded that the headache-ending effect was most likely caused by narrowing of the dilated arteries, which had caused pain by being overstretched.[28] They thereby refuted the sympathicotonic theories of the 1920s and concluded that ergotamine had a vasoconstrictive effect. As this study was published in 1938, Horton and Alvarez may have been unaware of this mechanism when they started their research and may have adhered to the vasoconstrictive theory of migraine (and CH). The 1939 paper by Horton, however, had already described that the pathogenesis of the pain most likely lies in the phenomenon of vasodilatation.

In June 1930, the results of an experimental study in cats by Harold Wolff and William Lennox (1884-1960) were published.[29] They conducted several experiments to determine the effect of variations in the oxygen and carbon dioxide content of the blood on the pial vessels. They concluded

that changing the oxygen concentration had a small but noticeable effect on the diameter of the pial vessels. An increase in oxygen concentration let to vasoconstriction, while a decrease in oxygen concentration let to vasodilatation.

It could be suggested that the use of oxygen was eventually based on this study, but the effects described by Wolff and Lennox were small and observed in pial vessels. Moreover, Horton did not mention the vasoconstrictive effect of oxygen until 1961.

As mentioned before, it is possible that Alvarez (and Horton) adhered to the vasoconstrictive theories of headache at the start of their research.

In the early 20th century, oxygen was frequently used as a treatment for angina pectoris, a condition known to be associated with vasoconstriction.[30] The effect of oxygen had been noted in 1900 by Steele.[31] Taking into account the well-known use of oxygen in angina pectoris, it is possible that Alvarez tried to use oxygen in migraine to treat the supposed hypoxia caused by vasoconstriction. This theory is supported by writings of Hans Curschmann (1875-1950) in 1926, cited by Richter.[27] Curschmann noted that people with migraine often tended to also have angina pectoris complaints. Moreover, they tended to have complaints of cold hands and feet, possibly caused by vascular spasm, which might also underly the migraine. This strengthens the idea that there was a theory about a relationship between angina pectoris and migraine. Therefore, it seems reasonable that the treatment for angina pectoris was also tried in migraine (and thereby CH) patients.

On a side note, it is interesting to note that Curschmann already described that smokers in particular were more prone to developing angina pectoris. This did not become common knowledge until the second part of the 20th century. In 1964, *The Reports of the Surgeon General on Smoking and Health* reported growing evidence of an increased risk of cardiovascular disease in smokers.[32] One of the earliest studies on this subject was done by English *et al.* He found that the incidence of coronary disease in male patients at the Mayo Clinic was about three times greater in cigarette smokers than in non-smokers in the 40-59-year age range.[33] Furthermore, Russek published a study in 1950, stating that 100% oxygen given via a face mask led to a more pronounced and longer duration of the ECG manifestations of myocardial ischemia and failed to prevent the onset or influence the duration of anginal pain. He therefore believed that oxygen should be contra-indicated for angina pectoris without hypoxaemia.[34]

The use of oxygen after Horton

In the years that followed Horton's publications, several studies reported the use of oxygen in the treatment of CH. Sjaastad mentioned a study, published in 1953, in which attacks provoked by nitroglycerin or histamine were successfully aborted by treatment with 100% oxygen.[35] In 1958, Friedman and Mikropoulos described that ergotamine appeared to be more effective than oxygen.[36] Nelson (1970) described oxygen to be fairly effective when given early and of little use when started

at the peak of an attack.[37] In 1976, Graham stated that patients had occasionally obtained relief of acute attacks by breathing 100% oxygen for 15 minutes (min).[38] The first systematic study on the effect of oxygen therapy in the acute treatment of CH attacks was done by Kudrow in 1981.[15] He took an interest in oxygen therapy after a letter published in the *JAMA* (1978) by optometrist JF Janks, who described in detail his personal experience with oxygen inhalation for acute cluster attacks.[39] In Kudrow's study, the effect of self-administrated oxygen, using a mask and at a flow rate of 7 L/min for 15 min, was compared with sublingual ergotamine administration. The results showed that oxygen administration at 7 L/min for 15 min and sublingual ergotamine administration were both effective in aborting CH attacks. Oxygen aborted more than seven out of ten attacks in 82% of the patients, ergotamine in 70%. Moreover, the response to oxygen was faster, with an average response time of 6 min. After 6 min only 28.2% of the ergotamine group attacks were aborted. The peak response time for sublingual ergotamine was between 10 and 12 min. When the side-effects and contra-indications were also taken into account, oxygen seemed to be the best choice for the treatment of a CH attack. However, Kudrow also described a rebound effect in oxygen users: a shorter time until the next attack after oxygen usage. This was found in 25% of the patients.[15] Not until after Kudrow's study was published, did oxygen therapy as an acute CH treatment seem to be on the rise. Results like these, however, were not found in following studies.

In his book on CH, Kudrow (1980) mentioned an earlier study on oxygen treatment that was also described in his 1981 article, in which fifty-two patients were treated with 100% oxygen for 15 min. He noted that 75% responded significantly. The worst responders were chronic cluster headache (CCH) patients over 49 years of age.[40] In a recent study, however, responders to oxygen seemed to be slightly older ($p = 0.11$) and percentages of episodic cluster headache (ECH) patients were equally distributed between the responder and non-responder group.[41]

Kudrow further described a study by Sakai and Meyer, who demonstrated that 100% oxygen, administered during an attack, promptly reduced cerebral blood flow and pain. It was suggested that there is a hyperreactivity of the cerebral blood vessels to oxygen in CH patients.[42]

In 1981 treatment with oxygen at 8 L/min was compared with the patients usual oral medication, such as ergot derivatives or analgesic tablets.[43] All but one patient noticed faster relieve when treated with oxygen compared with oral medication, and all twelve patients responded to oxygen treatment. A crossover study by Fogan (1985) between oxygen at 6 L/min and room air showed a highly statistically significant difference in pain relief scores. Fifty-six percent of patients experienced relieve in over 80% of attacks while using oxygen, compared with 7% using room air.[44] Nowadays, oxygen still is usually delivered at a flow rate of 7 L/min, as was done in the early study by Kudrow. A recent study was conducted with a higher oxygen flow rate, 12 L/min, which also appeared to be effective (Table 2).[16]

Table 2. Important data in the history of cluster headache in relation to oxygen

1900	Steele [31]	Oxygen as a treatment for angina pectoris
1926	Curschmann [27]	Co-morbidity of angina pectoris and migraine
1926	Harris [6]	First complete description of cluster headache (migrainous ciliary neuralgia)
1930	Wolff [29]	Effects of oxygen on cranial blood vessels
1938	Graham [28]	Effect of ergotamine injections most likely caused by vasoconstriction of the carotid arteries
1939	Horton [10]	First description of histaminic cephalgia
1940	Alvarez [19]	First description of oxygen as a treatment for headache. Good results in typical migraine
1952	Horton [1]	First description of oxygen as a treatment method for histaminic cephalgia
1955	Horton [20]	Review paper about oxygen treatment in 1176 patients with histaminic cephalgia
1981	Kudrow [15]	First systematic study on oxygen treatment for cluster headache Oxygen seemed equally or more effective than ergotamine
1985	Fogan [44]	Crossover study showed that oxygen was more effective than room air
2009	Cohen [16]	Oxygen at 12 litre/minute was proven more effective than room air

Hyperbaric oxygen treatment

Hyperbaric oxygen (HBO) in the treatment of CH has also been tried. Sjaastad mentioned a case report by Weiss *et al.* (1989),[45] who described the successful treatment of two attacks in a patient refractory to all other treatments. Unfortunately, the timing of the events was poorly described, and the possibility of spontaneous recovery, without an influence of HBO, could not be excluded.[35]

Following this case report several studies were conducted to explore the abortive and prophylactic effect of HBO in CH. Porta *et al.* (1991) conducted a crossover study between HBO treatment and normobaric oxygen treatment at a flow rate of 7 L/min for 15 min. Eight out of fourteen patients were 'partially refractory' or 'totally refractory' to normobaric oxygen. All fourteen patients achieved 'complete relief' within a few min after starting HBO treatment.[46]

Di Sabato *et al.* (1993) conducted a double-blind study comparing HBO with placebo. HBO resulted in an interruption of the current attack in six out of seven patients. Of the six patients in which HBO resulted in an interruption of the attack, three had no more attacks for a period lasting from 4 to 6 days, and the other three had no attacks during the entire follow-up period of 2 months. In the patients receiving placebo treatment the occurrence of successive attacks remained unmodified.[47]

Pascual *et al.* (1995) studied the effect of five to twenty sessions of HBO therapy on both the duration and frequency of CH attacks in four people with CCH. Two patients improved dramatically while on HBO treatment. This positive treatment effect remained for 2 and 31 days, respectively, after treatment. One patient noticed only a lower frequency of attacks and one patient noticed no effect at all.[48] A double-blind placebo crossover study by Nilsson Remahl *et al.* (2002) described a positive effect of both hyperbaric placebo and HBO treatment in six out of sixteen and five out of fourteen patients, respectively. The effect was mainly prophylactic and was thought to be caused by the hyperbaric condition itself, or by a marked placebo effect.[49]

A Cochrane review (2008) concluded that there is insufficient evidence to establish the effects

of HBO as a treatment for an acute CH attack or as prophylaxis.[50] Because of high costs and poor availability, the use of HBO for the abortive treatment of CH is not advised.

Oxygen and Migraine

As mentioned above, Alvarez described the successful treatment of migraine with oxygen in 1940.[19] Currently, oxygen treatment for migraine attacks is applied only sporadically. A Cochrane review in 2008 concluded that there was some evidence that HBO treatment was effective for the termination of acute migraine in an unselected population.[50] No evidence was found for a prophylactic effect of HBO. Given the costs and poor availability of HBO therapy, it was concluded that more research should be done on patients unresponsive to standard therapy. Few adequate studies on migraine and normobaric oxygen therapy, as conducted by Alvarez, were found. Two small studies comparing normobaric oxygen with HBO found normobaric oxygen to be ineffective in the treatment of migraine.[51, 52] Another study (1999), conducted for treatment of acute migraine headache, compared nitrous oxide with 100% oxygen.[53] No analgesic effects of oxygen were found in this study in a small group (n = 12). However, the flow rate at which oxygen was applied was not provided, which makes these results much less valuable. It is not clear where oxygen got lost as a treatment for migraine between 1940 (Alvarez) and today. It was not mentioned as a possible treatment method for migraine in a large review on the subject in 1985.[12]

In 1961, Horton also described treating vascular headaches other than CH with oxygen. The results of this treatment, however, were not reported.[14] It may be postulated that oxygen treatment might not cover the long duration of a migraine attack. Moreover, the use of acute medication in an occasional migraine attack might not cause any problems, but when using it to treat CH attacks, potentially occurring multiple times per day, this might give rise to adverse effects. As already described by Alvarez, oxygen therefore might be more useful in patients with daily attacks than in those with longer and less frequent attacks. An interesting note by Alvarez supporting this idea is that in some migraine patients the headache started to recur about an hour after they stopped oxygen treatment.[19] Furthermore, some of the patients had to continue treatment for an hour or two before the headache disappeared, which could of course cause much practical discomfort.

Conclusions

It seems that oxygen was first used in a period when the vasoconstriction theory of migraine or vascular headache reigned. An association with angina pectoris was probably made. Later it turned out that the situation was the opposite: in CH there is not vasoconstriction but vasodilatation, and the oxygen probably does not control hypoxia. Moreover, oxygen is not effective in vasoconstriction (without clear hypoxaemia) and in the case of angina pectoris might even cause more vasoconstriction. Even though it was based on what later appeared to be wrong assumptions, an effective treatment was found, the true mechanism of which we do not know even now.

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Chapter 3

Cluster headache and oxygen: is it possible to predict which patients will be relieved? A retrospective cross-sectional correlation study

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Abstract

Most cluster headache patients respond to oxygen therapy, but approximately 20% does not. The aim of the present study was to assess which factors differ between cluster headache patients who respond to oxygen therapy and those who do not. We included patients from the headache clinic of Atrium Medical Centre Heerlen (n = 53) and patients who responded to a cluster headache web-site (n = 62). Participants completed a questionnaire with questions on cluster headache and factors that might be of significance with respect to the response to oxygen. Non-responders had less often smoked in the past (p = 0.014), had longer cluster headache attacks (p = 0.049), and more often reported interictal headache (p = 0.02) than responders. Logistic regression analysis showed these variables to be independent risk factors for not responding to oxygen and a clinical prediction model is provided. The area under the receiver operating characteristic curve was 0.75. We conclude that cluster headache patients who smoked in the past, had shorter attacks and were pain-free interictally respond best to oxygen inhalation. The results did not provide clues for the mechanism of action of oxygen therapy.

Introduction

The clinical syndrome of cluster headache (CH) is a well defined type of primary headache for which the International Headache Society has composed a set of diagnostic criteria in the 'Second Edition of International Classification of Headache Disorders (ICHD-II)'.[1] One of the first successful acute treatments for CH was oxygen. In his 1956 publication on 'histaminic cephalgia', Horton stated that immediate use of 100% oxygen will alleviate a mild attack considerably.[2] Stimulated by a letter to the editor,[3] Kudrow took an interest in oxygen treatment for CH and conducted a trial in 1981.[4] Until recently, inhalation of 100% oxygen via a non-rebreathing mask at a flow rate of at least 7 litre/minute (L/min) for 20 minutes (min) was still recommended as one of the acute treatments.[5] However, 18-25% of patients do not experience successful or significant headache relief with 100% oxygen at a flow rate of 7-8 L/min given at pain onset for 15 min.[4, 6] Moreover, several disadvantages are associated with oxygen use, including the inconvenient equipment, the fire hazard (especially since two thirds to almost 80% of CH patients currently smoke [7]) and the risk of psychological dependence with fear of leaving the home.[8] Therefore, it may be useful to know in advance which patients are unlikely to respond. Although some data can be derived from a few studies,[4, 9, 10, 11] resulting in a variety of factors influencing the chance of an unfavourable response, this question has not been studied adequately.

In the present study our objective is to provide a clinical predictive model for oxygen response in CH patients. Which patient characteristics determine clinical response to oxygen in the acute treatment of CH?

Methods

We recruited CH patients from the headache clinic of the Atrium Medical Centre Heerlen (Atrium MC) and via a web-site created by the department of Neurology of the Academic Medical Centre of Leiden.

Study population

CH patients from the headache clinic of the Atrium MC were contacted to inform them about the study and to ask whether they were interested in participation. We also included patients who responded to a call for study participants on a CH web-site.

Of the 155 persons to whom questionnaires were sent 140 responded. The questionnaires were checked to verify the diagnosis of CH according to the ICHD-II criteria for CH.[1] Patients were included if they had used oxygen for the first time less than 10 years ago and if they fulfilled the ICHD-II criteria for CH. The only criterion of the ICHD-II criteria the participants did not have to fulfil was a duration of the attack to be maximum of 3 hours (h). Van Vliet *et al.* stated that the upper limit of a CH attack of 3 h may be too strict.[12] Therefore we also included patients who exceeded the upper limit of 3 h if the remaining symptoms were typical for CH. The upper limit of the maximal

duration of the attacks was 24 h to make a clear difference with hemicrania continua. Exclusion criteria were uncertainty about the diagnosis, the use of oxygen less than four times and an age under 18 years.

We included 115 patients. Written or verbal informed consent was obtained from all participating patients. The Local Ethics Committee of the Atrium MC approved this study. The study was registered in the Dutch Trial Register (NTR 1539). The selection of patients is shown in Figure 1.

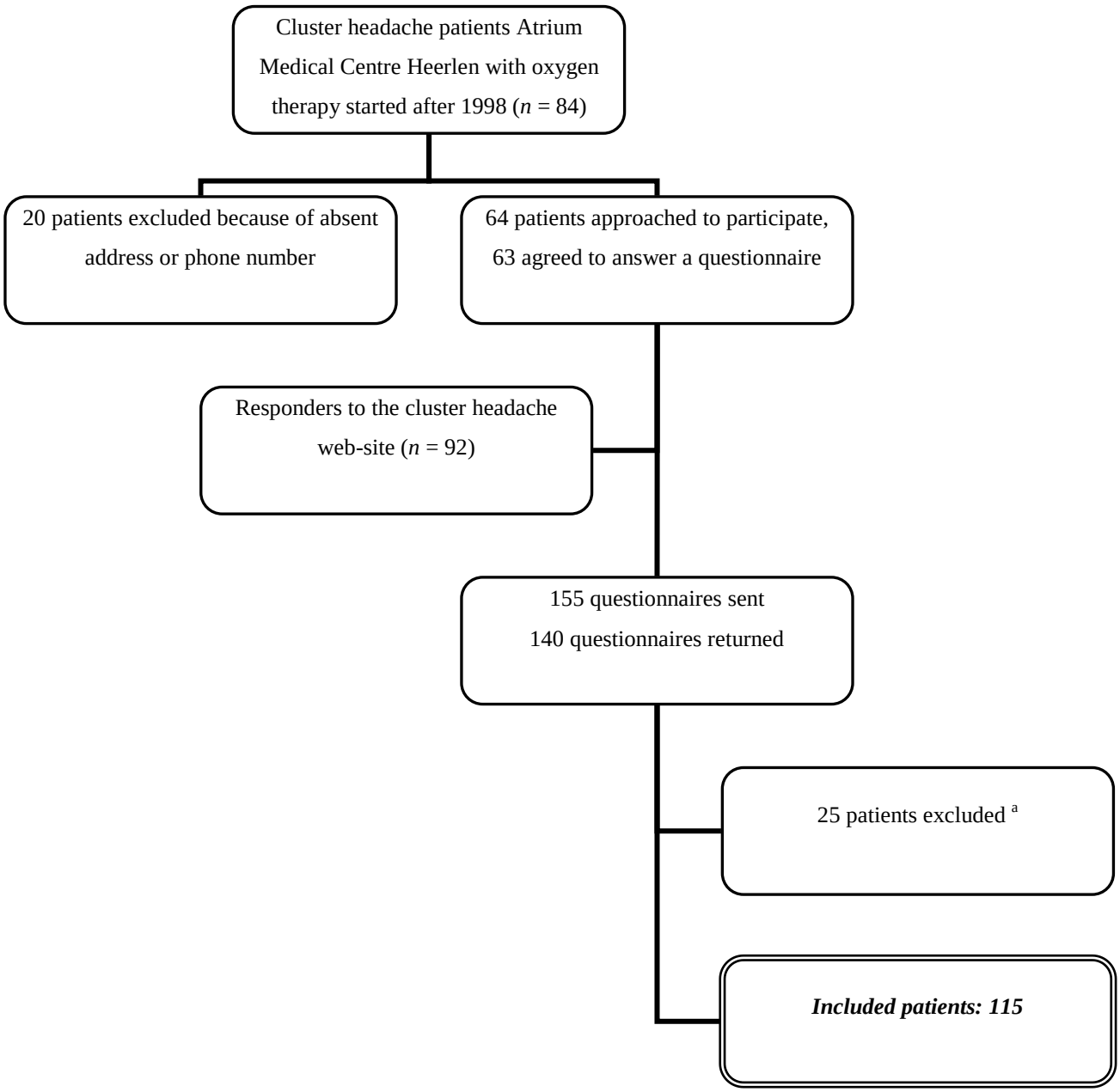

Figure 1. Patient flow chart

[a] Patients were excluded because they did not meet the ICHD-II criteria or they had not used oxygen at least three times

Study procedure

The participants completed a questionnaire consisting of items on patient and headache characteristics such as age, co-morbidities, smoking habits, alcohol use, duration and frequency of the attacks without medication effects and autonomic features. We especially paid attention to treatment and treatment response. We specifically asked to what extent the pain was relieved by using oxygen (with multiple choice answers: complete/much/little/none). If there was any doubt about the answers we contacted the participant by phone or e-mail to elucidate the answers. Moreover, we studied the medical files of the participants treated in the Atrium MC to see if the answers were matching. We contacted patients by phone to elucidate any inconsistencies.

The response to oxygen therapy was classified into five distinct groups as shown in Table 1. Clear responders were defined as patients who felt a reduction of pain on at least three occasions by at least 50% (complete or much relief) within 15 min after the start of oxygen inhalation. In the initial analysis we compared the clear responders with the clear non-responders plus the moderate responders (group A *versus* group B + C). We omitted group D from the initial analysis as the reaction to oxygen could have been mistaken for the natural course of the CH attack. Group E was left out because we believe this effect is not really beneficial. We also performed sub-analyses comparing the clear responders with the clear non-responders (group A *versus* group B), and comparing group A + E *versus* group B + C.

Table 1. Classification responders to oxygen

Group	Definition	*n*
A	Clear responders: A reduction of the pain on at least three occasions by at least 50% (complete or much relief) within 15 min after the start of oxygen inhalation	70
B	Clear non-responders: No or little effect of oxygen inhalation	19
C	Moderate responders: Some relief of oxygen but not fulfilling definition A	12
D	Responders to oxygen but reduction of the pain after more than 15 min	8
E	Responders fulfilling definition A, except for an increase in attack frequency after using oxygen	6

Statistics

We used descriptive statistics to summarise our variables including mean, standard deviation (SD), median, inter quartile ranges (IQR), frequencies and percentages. The percentages of dichotomous variables were compared using Chi-square tests. In case of low cell count (< 5 observations) we used Fisher's exact test. Non-normally distributes variables were analysed using the Mann-Whitney *U* test.

The continuous and normally distributed variables were compared using the Independent *t* test. All tests were two-tailed. The variables that showed significance in the single variable analysis were evaluated in the logistic regression analysis. We evaluated the predictive ability by determining the area under the receiver operating characteristic (ROC) curve. All analyses were performed using 'SPSS for Windows' version 16. The threshold of significance is $p < 0.05$ in all analyses.

Results

A total of 115 patients were included, of whom eighty-seven men (75.7%), giving a male-to-female ratio of 3:1. Mean current age was 47.9 years (SD 12.0) and mean age at onset of the CH symptoms was 37.0 (SD 14.4). The majority of the participants had episodic cluster headache (ECH) (73.4%). Eighty-nine of the 115 patients remembered the past oxygen flow rate, with a mean of 7.6 L/min (total range 2-15 L/min). Seventy-eight of these eighty-nine patients used a flow rate of more than 6 L/min, making the use of an oxygen face mask necessary.

Baseline characteristics

Only a few patient characteristics differ between the patients recruited from the Atrium MC and the patients recruited via the web-site (Table 2). One easily explicable difference is the number of diagnoses made by a neurologist, obviously because of the way the participants were recruited. All patients recruited from the headache clinic of Atrium MC were diagnosed by a neurologist, whereas only 54.1% of the patients recruited via the web-site were diagnosed by a neurologist. The remaining twenty-nine patients were diagnosed by a general practitioner or another physician. Two less obvious differences are the smoking habits and the use of alcohol. In the Atrium MC cohort significantly more patients currently smoke. In the web-site cohort significantly more patients are currently using alcohol and used alcohol in the past.

Because of the retrospective character of this study, we split the group of patients into one cohort with the use of oxygen for the first time less than 5 years ago and a cohort using oxygen for the first time 5-10 years ago and compared these cohorts. The rationale for this division was that we assumed a smaller risk of recall bias when the cohorts did not differ significantly. The only significant difference was the appearance of interictal headache, with the most recent cohort experiencing more interictal headache (58.3% *versus* 81.4%).

Based on these results we believe it was acceptable to lump together the cohorts Atrium MC, web-site, cohort 1999-2003 and cohort 2004-2009 and split the total group again in responders and non-responders to calculate the results.

Table 2. Comparison characteristics cohort Atrium Medical Centre Heerlen to cohort web-site

	Cohort Atrium MC (n = 53)	Cohort web-site (n = 62)	Significance (p value)
Men, *n* (%)	37 (69.8)	50 (80.4)	0.26 [a]
Age at onset cluster headache, mean (SD)	37.8 (13.5)	36.3 (15.1)	0.57 [b]
Diagnosis by neurologist, *n* (%)	53 (100.0)	33 (54.1)	< 0.001 [a]
Current smoking, *n* (%)	36 (67.9)	25 (40.3)	0.006 [a]
Past smoking, *n* (%)	47 (88.7)	51 (82.3)	0.42 [a]
Current consumers of alcohol, *n* (%)	29 (54.7)	49 (79.0)	0.01 [a]
Consumers of alcohol in the past, *n* (%)	32 (66.7)	54 (87.1)	0.02 [a]
Average attack duration (min)	80.00 (38-120)	90.00 (45-158)	0.44 [c]
No interictal headache, *n* (%)	35 (66.0)	40 (65.6)	1.00 [a]
Episodic cluster headache, *n* (%)	35 (66.0)	50 (80.6)	0.12 [a]
Age at start oxygen therapy, median (IQR)	42.00 (37-52)	47.00 (33-52)	0.78 [b]
Years between onset of cluster headache and start of oxygen therapy, median (IQR)	3.00 (0.25-8)	5.00 (2-12)	0.09 [c]
Responders, *n* (%)	33 (62.3)	37 (59.7)	0.91 [d]

[a] Chi-square test, continuity correction, [b] Independent samples *t* test, [c] Mann-Whitney *U* test, [d] Pearson Chi-square

Univariate analysis

Patient and headache characteristics of the responders (group A) and non-responders (group B + C) are shown in Tables 3 and 4. A significant difference with respect to patient characteristics between responders and non-responders is smoking in the past. There are more smokers in the responders group compared to the non-responders. The percentages of consumers of alcohol do not differ, however, there is a difference in the number of alcoholic drinks consumed in responders who use alcohol compared with non-responders who use alcohol. This difference is also not statistically significant.

Table 3. Comparison patient characteristics responders and non-responders

	Responders (n = 70)	Non-responders (n = 31)	Significance (p value)
Men, *n* (%)	50 (71.4)	24 (77.4)	0.70 [a]
Current age, mean (SD)	49.29 (12.21)	45.26 (10.10)	0.11 [b]
Number of participants currently older than 49, *n* (%)	40 (57.1)	13 (41.9)	0.23 [a]
Age at onset CH, mean (SD)	38.47 (15.22)	35.33 (11.42)	0.26 [b]
Number of participants older than 49 at onset CH, *n* (%)	21 (30.0)	6 (19.4)	0.38 [a]
Diagnosis by neurologist, *n* (%)	49 (71.0)	25 (80.6)	0.44 [a]
Current BMI, median (IQR)	26.00 (23-29)	25.00 (22-28)	0.24 [c]
BMI at onset CH, median (IQR)	24.00 (22-26)	24.00 (23-26)	0.97 [c]
Current smoking, *n* (%)	37 (52.9)	14 (45.2)	0.62 [a]
Past smoking, *n* (%)	63 (90.0)	21 (67.7)	***0.014*** [a]
Pack years per smoker, median (IQR)	21.50 (15-32)	22.5 (15-34)	0.95 [c]
Current consumers of alcohol, *n* (%)	49 (70.0)	18 (58.1)	0.35 [a]
Consumers of alcohol in the past, *n* (%)	53 (79.1)	21 (72.4)	0.65 [a]
History of sleep apnoea, *n* (%)	5 (7.1)	0 (0)	0.32 [d]
History of other headache disorder(s), *n* (%)	20 (28.6)	13 (41.9)	0.28 [a]
History of trauma capitis, *n* (%)	20 (28.6)	10 (32.3)	0.89 [a]
Positive family history, *n* (%)	4 (5.7)	3 (9.7)	0.67 [d]

[a] Chi-square test, continuity correction, [b] Independent samples *t* test, [c] Mann-Whitney *U* test, [d] Fisher's exact probability test two-sided, [e] Pearson Chi-square

Table 4. Comparison headache characteristics responders and non-responders

	Responders (n = 70)	Non-responders (n = 31)	Significance (p value)
Attack duration without medication (min)			
Average duration, median (IQR)	70.00 (38-120)	90.00 (45-180)	0.13 [c]
Minimal duration, median (IQR)	30.00 (20-60)	60.00 (30-105)	0.08 [c]
Maximal duration, median (IQR)	120.00 (64-180)	210.00 (90-270)	***0.049*** [c]
Maximal duration of attacks > 180 min, *n* (%)	13 (18.6)	14 (45.2)	***0.011*** [a]
No interictal headache, *n* (%)	52 (75.4)	15 (48.4)	***0.02*** [a]
Episodic cluster headache, *n* (%)	54 (77.1)	23 (74.2)	0.95 [a]
Autonomic features			
Conjunctival injection, *n* (%)	57 (82.6)	23 (76.7)	0.68 [a]
Lacrimation, *n* (%)	65 (94.2)	28 (90.3)	0.67 [d]
Nasal congestion, *n* (%)	48 (69.6)	22 (71.0)	1.00 [a]
Rhinorrhea, *n* (%)	49 (72.1)	20 (69.0)	0.95 [a]
Ptosis, *n* (%)	47 (69.1)	23 (76.7)	0.60 [a]
Miosis, *n* (%)	48 (82.8)	16 (72.7)	0.36 [d]
During attacks			
Nausea/vomiting, *n* (%)	14 (20.0)	11 (36.7)	0.13 [a]
Photo-/phonophobia, *n* (%)	45 (64.3)	21 (67.7)	0.91 [a]
Restlessness, *n* (%)	55 (78.6)	29 (93.5)	0.12 [a]

[a] Chi-square test, continuity correction, [b] Independent samples *t* test, [c] Mann-Whitney *U* test, [d] Fisher's exact probability test two-sided, [e] Pearson Chi-square

The attacks of CH last longer in non-responders, with a significant difference in the maximum attack duration. In Table 4 and Figure 2 the attack duration without medication effects is shown. In responders 18.6% and in non-responders 45.2% exceeded the upper limit of 180 min in the attacks which the patients themselves experienced as extremely long. In average attacks only 16.8 % exceeded this limit.

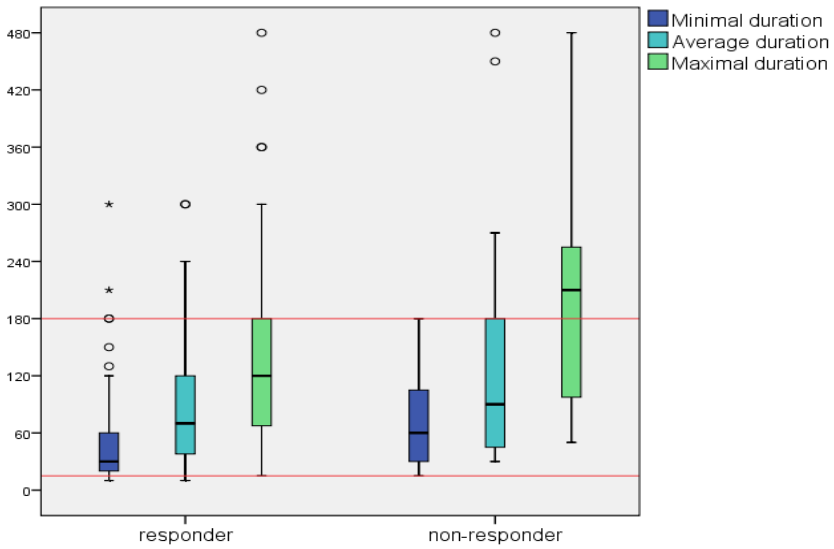

Figure 2. Attack duration in minutes (median)

The *coloured boxes* represent the attack duration in 50% of the participants, the *vertical line* is the near total spreading. The *dots* and *asterisks* are the extreme values. We omitted the three most extreme measures from this figure to enhance the clarity. Two of the omitted values were maximal durations of the attacks in responders (960 and 1,440 min), one was a maximal duration of the attack in a non-responder (1,440 min)

Another significant difference is the amount of participants who reported to experience interictal pain. Of all responders, 75.4% does not experience headache between the CH attacks. Only 48.4% of the non-responders are pain free interictally. Non-responders more often feel nauseous or restless, but this difference did not reach statistical significance.

We also asked ECH sufferers how long a cluster period lasts on average, minimally and maximally. In contrast with the attack duration, cluster periods lasted longer in responders compared to non-responders. This difference is not statistically significant. No differences were found in attack frequency, duration of remission period or frequency of cluster periods. In chronic cluster headache (CCH) patients there was no difference in cluster attack frequency in responders compared to non-responders.

Other than the patient and headache characteristics, the questionnaire also contained items on the oxygen, other acute and prophylactic treatments as described above; this is summarized in Table 5. Responders had a higher age when starting with oxygen ($p = 0.18$). There was no difference in the number of years between the onset of the CH symptoms and the start of oxygen therapy; the patients reported a median of 4 years in responders and a median of 3 years in non-responders. Most patients started oxygen therapy immediately after the onset of an attack. Non-responders to oxygen reported significantly more relief from triptan use. Responders more often use verapamil (84.1 % compared to 66.7 % in non-responders, $p = 0.09$). Other prophylactic treatments which were used were prednisone

(*n* = 12), methysergide (*n* = 6), lithium (*n* = 3) and ergotamine (*n* = 1). Groups using these other prophylactic treatments were too small for statistical analysis.

Table 5. Comparison cluster headache therapy responders and non-responders

	Responders (*n* = 70)	Non-responders (*n* = 31)	Significance (*p* value)
Age at start oxygen therapy, median (IQR)	45.0 (12.5)	41.6 (9.5)	0.18 [a]
Years between onset of cluster headache symptoms and start of oxygen therapy, median (IQR)	4.00 (1-9)	3.00 (0-12)	0.74 [b]
Oxygen dose > 10 L/min, *n* (%)	3 (5.3)	3 (11.1)	0.38 [d]
Minutes until start of oxygen therapy after onset of cluster headache symptoms, median (IQR)	1.00 (1-5)	1.00 (1-5)	0.77 [b]
Triptan users, *n* (%)	55 (78.6)	27 (87.1)	0.46 [c]
Good response to triptans (much or total relieve of pain), *n* (%)	38 (69.1)	24 (92.3)	***0.04*** [a]
Verapamil users, *n* (%)	58 (84.1)	20 (66.7)	0.09 [c]
Good response to verapamil (much or total relieve of pain), *n* (%)	21 (38.9)	9 (49.4)	0.71 [a]

[a] Chi-square test, continuity correction, [b] Independent samples *t* test, [c] Mann-Whitney *U* test, [d] Fisher's exact probability test two-sided, [e] Pearson Chi-square

Univariate sub-analysis

Next to the initial analysis described above, we made a sub-analysis. In sub-analysis part 1 we compared group A (*n* = 70) with group B (*n* = 19), so the clear responders *versus* the clear non-responders. In sub-analysis part 2 we compared group A + E (*n* = 76) with group B + C (*n* = 31), so the clear responders plus the patients with an increase in attack frequency using oxygen *versus* the clear non-responders plus the moderate responders. In sub-analysis part 1 the only two variables which reached significance are shown in Table 6. The difference in interictal pain was also seen in the initial analysis. Significantly more non-responders reported nausea and vomiting (50% compared to 20% of the responders), a difference we did not find in our initial analysis.

Table 6. Significant differences in sub-analysis part 1

	Responders (n = 70)	Non-responders[a] (n = 19)	Significance (p value)
No interictal headache, *n* (%)	52 (75.4)	8 (42.1)	0.01 [b]
Nausea/vomiting, *n* (%)	14 (20.0)	9 (50.0)	0.02 [c]

[a] Non-responders here consisting of only clear non-responders (group B), leaving group C out of the analysis,
[b] Chi-square test, continuity correction, [c] Fisher's exact probability test two-sided

When comparing group A + E *versus* group B + C in sub-analysis part 2 we did not find any other significant values or differences than we found in our initial analysis.

Multivariate analysis

Three variables that were significant in the initial univariate analysis are smoking in the past, interictal headache and maximal duration of the CH attack (especially attacks longer than 180 min). We performed logistic regression analysis to test if these variables are independent risk factors for responding or non-responding to oxygen.

Table 7 shows that all the variables contribute significantly to this model, even if we adjust for the other variables in the model, so these variables are independent risk factors for responding or non-responding to oxygen. The odds ratios are also presented in the table. The presence of every one of the three variables, smoking in the past, no interictal headache and a maximal attack duration of 180 min or less, gives patients approximately a three to four times higher odds of being a responder than being a non-responder.

Table 7. Multivariable predictors for oxygen responders in cluster headache patients

	Odds ratio	95% CI	Significance
Smoking in the past, *n* (%)	3.99	1.24-12.80	***0.020***
No interictal headache, *n* (%)	3.26	1.24-8.57	***0.016***
Maximal attack duration $\leq$ 180 min	3.84	1.40-10.57	***0.009***

We evaluated the predictive ability of our set of variables for responding to oxygen by determining the area under the ROC curve, shown in Figure 3. The area under the ROC curve was 0.75, indicating a fair discrimination of the final model.

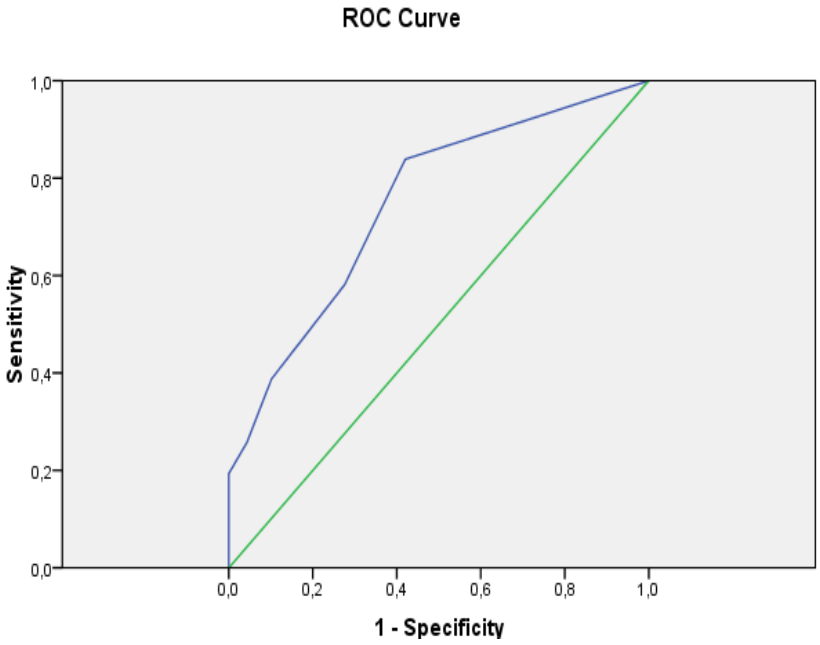

Figure 3. Receiver operating characteristic curve

Area under ROC Curve is 0.75

Finally, we studied the relationship between interictal pain and severity of CH. We found that interictal pain is an independent predictor of oxygen response instead of being the consequence of the severity of CH. Biserial correlation coefficients were assessed. The correlation coefficient of interictal pain and attack frequency was 0.08 at a significance level of 0.95; the correlation coefficient of interictal pain and severity of a CH attack was 0.04 at a significance level of 0.99. Therefore, no correlation between interictal pain and severity of CH could be established.

Discussion

In this study of 115 CH patients who used oxygen, we identified three predictors of poor oxygen response, notably no smoking in the past, interictal headache, and a maximal attack duration of more than 180 min. The presence of each variable gives patients approximately a three to four times higher odds of being a non-responder than being a responder.

Currently, it is not fully known which characteristics predict response to oxygen in CH patients. Table 8 shows factors that have been associated with an unfavourable response in previous studies.[4, 9, 10, 11] In a recent study, restlessness (OR 0.09, $p = 0.019$) and nausea/vomiting (OR 0.41, $p = 0.029$) were identified as negative predictors of oxygen response. It was hypothesized that the oxygen face mask is not tolerated in some restless patients.[10] Restlessness and nausea/vomiting during a CH attack were reported by 67.9% and 27.8 % of the patients, respectively.[9] One study found women having significantly more often nausea (62.5% *versus* 43.5%, $p = 0.09$) and vomiting (46.9% *versus* 17.4%, $p = 0.003$) than men. In this study, an oxygen treatment response of only 59.1% in women was found

compared to 87% in men. This difference is significant ($p = 0.01$).[11] Other studies did not identify gender as a predictor of response to oxygen therapy.[4, 9, 10]

Seventy-five percent of women *versus* 61% of men reported a smoking history.[13] Current smoking was not identified as a statistically significant negative predictor of oxygen response.[10] There were statistically significantly more men than women smoking currently.[9]

One trial found significantly better effects of oxygen inhalation in ECH patients under 50 years of age compared to CCH patients over 49 years of age ('treatment successes' of 92.9% and 57.1% respectively, $p < 0.05$). There was no significant response difference between patients under 50 years of age and patients over 49 years of age, neither was there between ECH and CCH patients of all ages.[4] Likewise, a more recent study did not identify age and ECH (%) as statistically significant negative predictors of oxygen response.[10]

One author noted that in some unresponsive cases acute CH attack treatment had been started late.[4] Another study group stated it was less obvious whether the timing of acute treatment influences treatment success.[10]

Table 8. Factors associated with an unfavourable response to oxygen in cluster headache attacks from previous studies.[4, 9, 10, 11]

Factors	*p* value
Restlessness [10]	0.019
Chronic cluster headache and > 49 years of age [4]	< 0.05
Females [4, 9, 10, 11]	0.01 – 'no significance'
Nausea and vomiting [10, 11]	0.029

Smoking as a predicting factor for oxygen response was mentioned in two previous studies. We also could not identify *current* smoking as a statistically significant negative predictor of oxygen response. However, in contrast to the previous finding of women responding less to standard oxygen therapy and having a higher past smoking percentage than men,[13] we clearly found absence of past smoking to be a predictor of poor oxygen response. It is difficult to explain this finding. Smaller changes in cerebral gray matter blood flow during inhalation of 100% oxygen in chronic cigarette smokers compared to non-smokers suggest decreases in vasoconstrictor capacitance among smokers. In their discussion, the authors also mention that chronic cigarette smoking disrupts the normal balance between vasodilator prostacyclin and vasoconstrictor thromboxane A2 in favour of vasoconstriction.[14] However, increases in middle cerebral artery flow velocity and a reduced cerebrovascular resistance caused by (current/active) smoking have been found in two other studies.[15, 16] In one of these, identical decreases in middle cerebral artery flow velocity during hyperoxia in smokers and non-smokers were

demonstrated.[16] We conclude that the (although conflicting) results at least do not endorse an excessive cerebral blood flow reduction in smokers in response to hyperoxia, as suggested by our results.

In the present study, significantly more responders do not experience interictal headache. However, when comparing the 1999-2003 cohort to the 2004-2008 cohort, we found patients reporting significantly less interictal headache and having a slightly (not significantly) higher responder percentage (69.8%, compared to 55.6%) in the 1999-2003 cohort. Therefore, recall bias could be involved. Another explanation could be that a number of patients who experience interictal headache are misdiagnosed hemicrania continua patients with fluctuations in headache intensity, and therefore respond less to oxygen inhalation. However, approximately three-quarters of the responders and non-responders have ECH. In non-responding ECH patients, the duration of the cluster period was 1.00-2.63 months. Therefore, besides an unknown reaction to indomethacin, the diagnosis of hemicrania continua is unlikely because of a headache duration of less than 3 months.[1] Furthermore, the majority, if not all, patients are able to delineate attacks from interictal pain, as experienced in clinical practice. Finally, it could be the effect of oxygen itself to stop the CH attack and subsequently prevent the occurrence of interictal headache possibly following an ongoing CH attack. We found this effect of oxygen to be independent of the severity of CH, measured by attack frequency and severity of a CH attack.

We included patients who exceeded the upper limit of attack duration of 3 h if the remaining symptoms were typical for CH. We found 26.7 % of the responding and non-responding patients reporting their longest attacks lasting more than 180 min. Only 16.8% reported their attacks of average duration lasting more than 180 min. In one study 12.7 % of CH patients exceeding the average 3 h limit was found.[12] In another, only 7.3% of the patients had a CH attack duration of more than 180 min.[9] It is remarkable that two of three patients with maximal attack durations exceeding 8 h were responders. These three patients reported an average attack to last only 150-180 min. Therefore, oxygen may prevent CH attacks to last extremely long, but variance in effect between attacks in one patient is possible. Because of exclusion in the univariate analysis of patients experiencing an increase in attack frequency using oxygen, the variance cannot be attributed to rebound CH. Logistic regression analysis showed a maximal attack duration of more than 180 min to be a predictor of poor oxygen response, independent of the occurrence of interictal headache.

In summary, we conclude that the more typical CH patients, *i.e.* (past) smokers, having attacks lasting less than 180 min without interictal headache, respond best to oxygen inhalation.

An area under the ROC curve of 0.75 indicates that, besides our model, other factors are involved as well. Alternative factors to predict poor oxygen response found in previous studies were restlessness, nausea/vomiting, female gender and CCH in combination with an age of more than 49 years.[4, 9, 10, 11] Although we also found more non-responders reporting restlessness and nausea/vomiting, this

difference did not reach significance in the initial univariate analysis. But when comparing the clear responders to the clear non-responders in the first part of the univariate sub-analysis, we also found significantly more non-responders reporting nausea and/or vomiting. Stimulation of certain areas of the hypothalamus can cause vomiting by unknown but probably direct neural connections with the vomiting centre located bilaterally in the medulla. Nausea is caused by excitation of certain portions of the vomiting centre or a closely associated area of the medulla.[17] The exact triggering site for nausea and vomiting in CH attacks is unknown. We were unable to confirm gender as a predictor of oxygen response.

Unfortunately, we were unable to include enough patients to compare ECH patients under 50 years of age to CCH patients over 49 years of age, as was done in a previous study.[4] In our study, responders to oxygen seem to be slightly older ($p = 0.11$); the percentages of ECH patients in the responder and non-responder group were almost equal.

In one study it was noted that in some cases unresponsive to oxygen (or ergotamine), the acute CH attack treatment had been started late.[4] In our study most patients started oxygen use immediately after onset of the attack, so we cannot judge the influence of delay on the effect.

We found that the majority of the patients used oxygen at a flow rate of approximately 7 L/min, using an oxygen face mask. This is consistent with the Dutch guidelines for CH that have advised (since 1997) using 6-7 L/min using an oxygen face mask.[18] It was based on trials (of Kudrow [4] and Fogan [19]), showing successful relief using this flow rate. Suggestions to use higher flow rates came in 2004, when Rozen reported three patients in whom a flow rate of 14-15 L/min was successful after initial failure with 7-10 L/min.[13] The suggestion was confirmed on a larger scale by a recent trial in which a flow rate of 12 L/min was used.[20]

A difference we found in the present study is that non-responders to oxygen report significantly more relief from triptan use. Because of the retrospective character of this study, patients may have used oxygen and triptans together, so one may assume that the effect of triptans is less clear in responders. Moreover, the placebo effect of triptans, which is known to be large in headache patients,[21, 22]could be more manifest in non-responders to oxygen.

Furthermore, we found oxygen-responders using verapamil more often ($p = 0.09$). Because of the retrospective character, time relationship between start of oxygen treatment and start of prophylactic verapamil treatment could not be adequately studied in all patients. However, it may be assumed that the majority of the patients in this study started verapamil and oxygen simultaneously, as such has been described in the Dutch guidelines for CH since 1997.[18] Like clinical practice in migraine patients, this finding suggests that CH patients who use prophylactic medication are more responsive to acute therapies. However, a pilot study on topiramate prophylaxis and triptan response in migraine patients was unable to confirm this.[23]

An interesting finding headache specialists sometimes observe in daily practice was reported by six of our participants, who responded well to oxygen but noticed an increase in attack frequency when using oxygen to abort an attack. In some of these patients oxygen seemed not to abort the attack but rather to postpone it instead. Twenty-five percent of the patients in a previous trial experienced rebound cluster attacks.[4] The EFNS guideline correctly states oxygen use should be restricted in cases in which oxygen delays rather than aborts the attack.[24] More research on this subject is obviously necessary.

One of the limitations of the present study is the retrospective character with a risk of recall bias. We tried to reduce this risk by comparing patients who used oxygen for the first time less than 5 years ago with patients who used oxygen for the first time 5 to 10 years ago. Another limitation is the use of questionnaires completed by the patients themselves. However, CH is a revolting pain which patients seem to remember accurately. Moreover, we compared given answers to medical files and contacted patients to elucidate unclear answers or inconsistencies. Finally, we compared the baseline characteristics of our study population to those previously studied and these appeared to be consistent.[9] Therefore, we believe that our data represent accurate findings.

Obviously, a larger study population would have allowed us to analyse all our near significant variables in the logistic regression analysis.

Conclusion

No smoking history, interictal headache, and a maximal attack duration of more than 180 min were identified as predictors of a poor oxygen response. The presence of each variable gives patients approximately a three to four times higher odds of being a non-responder than being a responder Although in daily practice oxygen should not be withheld if unfavourable factors are present, the information could be discussed with the individual patient when an acute CH treatment is prescribed. To analyse all our near significant variables and abort the risk of recall bias, a more refined prospective multi-centre study would be necessary.

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Chapter 4

Cluster headache and oxygen: is it possible to predict which patients will be relieved? A prospective cross-sectional correlation study

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Abstract

Response to 100% oxygen as acute treatment for cluster headache is relative low considering certain subgroups or predictors. The primary purpose of the present study was to find prospectively which factors differ between responders and non-responders to oxygen therapy. The second goal was to find whether any of these differences would clarify the mechanism of pain reduction by oxygen and cluster headache pathophysiology.

Patients diagnosed with cluster headache according to the ICHD-II criteria, who started on oxygen therapy (n = 193), were recruited from 51 outpatient clinics and via patient web-sites in The Netherlands. Patients had to return two questionnaires around the start of oxygen therapy (n = 120). Eventually, 94 patients were included.

Clear non- plus moderate responders had ever used pizotifen more often (p = 0.03). Clear non-responders more often had photophobia or phonophobia during cluster headache attacks (p = 0.047) and more often had used triptans in the same active phase as the phase in which they had used oxygen for the first time (p = 0.02). Using correction for multiple testing, we could only confirm a statistical significant difference in triptan use.

We were unable to locate the level of action of oxygen in the thalamus and cortex or confirm the sites of its action presently known, solely based on current knowledge of photophobia circuits. However, we conclude that particularly the higher frequency of photophobia or phonophobia in clear non-responders deserves further study to understand the mechanism of pain reduction by oxygen and cluster headache pathophysiology.

Introduction

Cluster headache (CH) is one of the trigeminal autonomic cephalalgias (TACs). Attacks are characterised by severe unilateral pain, mostly located in the first trigeminal division and lasting 15-180 minutes (min), associated with at least one ipsilateral autonomic feature and/or restlessness or agitation.[1] Inhalation of 100% oxygen via a non-rebreathing mask with a flow rate of at least 7 litre/minute (L/min) is one of the acute attack treatments.[2] Successful relief inhaling normobaric 100% oxygen, administered through a facial mask at a flow rate of respectively 7, 6, and 12 L/min for 15 min was proven in three trials.[3, 4, 5] Percentages of successful treatment were 75% and 82% of CH patients using 7 L/min [3] and percentage of pain freedom at 15 min was 78% of oxygen treated CH attacks using 12 L/min, the latter being significantly better than high-flow air placebo ($p < 0.001$).[5] Response to 100% oxygen is more variable when other study types and/or subgroups or predictors are considered.[3, 6, 7, 8, 9] Most extreme oxygen responses at the lower end were found in non-placebo controlled studies in the subgroup of chronic cluster headache (CCH) patients aged older than 49 years (percentage of successful treatment of 57%) [3] and for the predictor restlessness (Odds ratio (OR) for oxygen response of 0.10).[8] Lower oxygen responses can be of clinical significance, because oxygen use has several disadvantages, such as a fire hazard and rebound CH, as we demonstrated in a recent study.[10] To provide a clinical prediction model for oxygen response in CH patients, we performed a retrospective cross-sectional correlation study. Variables predicting non-response to oxygen were: no smoking history (OR 3.99), interictal headache (OR 3.26) and a maximal attack duration of more than 180 min (OR 3.84). Particularly in patients with one or more of these characteristics, this information could be discussed before oxygen prescription.[11]

At present, little is known about CH pathophysiology and the mechanism of action of oxygen. A dysfunction in the interactions between brain areas of the pain matrix might produce a permissive state, resulting in disinhibition of the hypothalamo-trigeminal pathway and thus a pain attack. Ipsilateral parasympathetic symptoms could be caused either by a direct hypothalamic effect or by peripheral stimulation of parasympathetic efferents of the superior salivatory nucleus (SSN).[12] Oxygen is suspected to produce cerebral vasoconstriction. It can produce cerebral vasoconstriction centrally at brain stem level via inhibitory effects on the cranial parasympathetic vasodilator pathway.[13] Furthermore, oxygen can produce cerebral vasoconstriction peripherally at a vascular level via direct potentiation of the constrictive effect of catecholamines and 5-hydroxytryptamine (5-HT) on muscle or the indirect Pasteur effect,[14] or via decrease in the trigeminal released calcitonin gene-related peptide (CGRP) concentration.[15] However, oxygen induced vasoconstriction is probably not the only factor responsible for pain relief.[16] Another vasoactive pathophysiological mechanism, in a more or lesser way related to vasoconstriction, is the anti-inflammatory role hyperoxia has in neurogenic inflammation.[17] The variables predicting non-response to oxygen in our retrospective study did not learn us more about mechanisms of action of oxygen and, therefore, CH pathophysiology.[11]

In order to analyse near significant variables of the retrospective cross-sectional correlation study [11] and to abort the risk of recall bias, we have studied the factors which differ between responders and non-responders to oxygen therapy in a prospective study design. The second goal of this prospective study was to find whether any of these differences would clarify the mechanism of pain reduction by oxygen and CH pathophysiology.

Methods

Patient recruitment

We recruited CH patients from 51 outpatient clinics and via advertisements placed on two patient web-sites in The Netherlands. Patients were recruited between October 2009 and February 2013.

Study population

Patients diagnosed with CH according to the ICHD-II criteria [1] (except for the criteria of a maximum attack duration of 180 min if untreated [18] and a maximal attack frequency of eight per day (if the average attack frequency was eight or less per day)), who started on oxygen therapy, were included. Oxygen and its preferred flow rate was prescribed by the patient's neurologist. Exclusion criteria were: age under 18 years, uncertainty about the diagnosis, previous use of oxygen therapy as attack treatment for headache and present use of oxygen therapy in less than three CH attacks. The study used two questionnaires. The first questionnaire contained questions to verify the ICHD-II diagnosis of CH. The combined first and second questionnaires contained questions asking about exclusion criteria. All neurologists and neurology registrars in The Netherlands were informed by letters and an e-mail about the inclusion criteria and two of the exclusion criteria (age under 18 years and previous use of oxygen therapy as attack treatment for headache).

Study procedure

Following study application, the first questionnaire was sent to the patient. This first questionnaire contained questions about smoking, alcohol consumption, other medical diagnoses, family history, medication use, CH characteristics and the influence of CH on daily activities. The second questionnaire was sent to the patient 1 month after the first questionnaire. This second questionnaire contained different questions about oxygen use, effects of oxygen use and medication use. In case questionnaires were not returned by the patient, they were sent to the patient again with monthly intervals, up to a maximum of three times for the first questionnaire (*i.e.* 2 months after the first sending). If there was any doubt about answers, inconsistency in answers or an unanswered question, the patient was contacted by phone or e-mail for elucidation.

To enable a comparison with our retrospective cross-sectional correlation study,[11] response to oxygen was classified in the same five groups, as shown in Table 1. Clear oxygen responders were defined as patients, who have experienced a pain reduction of at least 50% within 15 min after the start

of oxygen inhalation in at least three CH attacks. In the initial analysis we compared the group of clear responders (group A) with the combined group of clear non-responders (group B) and moderate responders (group C). In the sub-analysis we compared the group of clear responders (group A) with the group of clear non-responders (group B). In both analyses we left the groups oxygen responders with response after more than 15 min (group D) and with an increase in attack frequency (group E) out of the comparison, because the oxygen responses in both groups are not considered beneficial and because there is no clear distinction with the natural course of a CH attack in group D. Furthermore, we did not perform a sub-analysis comparing the combined group of the clear responders (group A) and oxygen responders with an increase in attack frequency (group E) with the combined group of clear non-responders (group B) and moderate responders (group C), because this sub-analysis revealed no new significant factors in our retrospective cross-sectional correlation study.[11]

Table 1. Classification of response to oxygen

Group	Name	Definition	*n*
A	Clear responders	Pain reduction of at least 50% within 15 min after the start of oxygen inhalation (or within 20 min after the start of 15 min of oxygen inhalation) in at least three cluster headache attacks	41 (3) [a]
B	Clear non-responders	Little or no effect of oxygen inhalation	19
C	Moderate responders	Some relief of oxygen, but not fulfilling definition A, D and E	12
D	Late responders	Pain reduction of at least 50%, more than 15 min after the start of oxygen inhalation (or at least 50% pain reduction within 20 min after the start of at least 16 min of oxygen inhalation)	18 (4) [a]
E	Patients with tendency to rebound cluster headache	Pain reduction of at least 50% within 15-20 min after the start of oxygen inhalation with an increase in attack frequency following oxygen use	4

[a] Values in brackets are the numbers of patients fulfilling the definitions in brackets. These numbers are included in the group totals of 41 for group A and 18 for group D.

Statistics

To summarize values of continuous variables we used means and medians as measures for central tendency and standard deviations (SD) and interquartile ranges (IQR) as measures of dispersion respectively. To summarize values of categorical variables we used sums (*n*) and percentages (%). To test whether the distribution of continuous variables was normal we used the Kolmogorov-Smirnov test in combination with the Q-Q Plot. Values of continuous and normally distributed variables were compared using the Independent samples *t* test. Values of continuous and non-normally distributed variables were compared using the Mann-Whitney *U* Test. Sums and percentages of the (dichotomous) categorical variables were compared using the Fisher's exact test in case of at least one observed

and/or expected cell count of five or less and the Chi-square test in case of all cell counts of more than five. All tests were two-tailed. The threshold for significance was $p < 0.05$. In a post-hoc analysis we used the Bonferroni correction with a threshold for significance calculated by the formula $p <$ (0.05/number of related variables). The number of related variables was set at four for variables concerning prophylactic medication, two for variables concerning acute medication and three for variables concerning photophobia and/or phonophobia. All analysis were performed using 'IBM SPSS Statistics 21 for Windows'.

Ethics

The study was approved by the local ethics committee. Written or verbal informed consent was obtained from all patients.

Results

Patient selection and inclusion

Of the 193 patients who entered the study (of whom 169 (87.6%) following initial screening by the patient's neurologist or neurology registrar), questionnaires were sent to 192. Both questionnaires were returned by 120 patients (response rate of 62.5%). Subsequently, a second screening using the inclusion and exclusion criteria was performed. Twenty-six patients were excluded and ninety-four patients were included. Of these ninety-four patients, ninety-two (97.9%) were known to have been treated by a neurologist or neurology registrar. Patient selection and inclusion is shown in Figure 1.

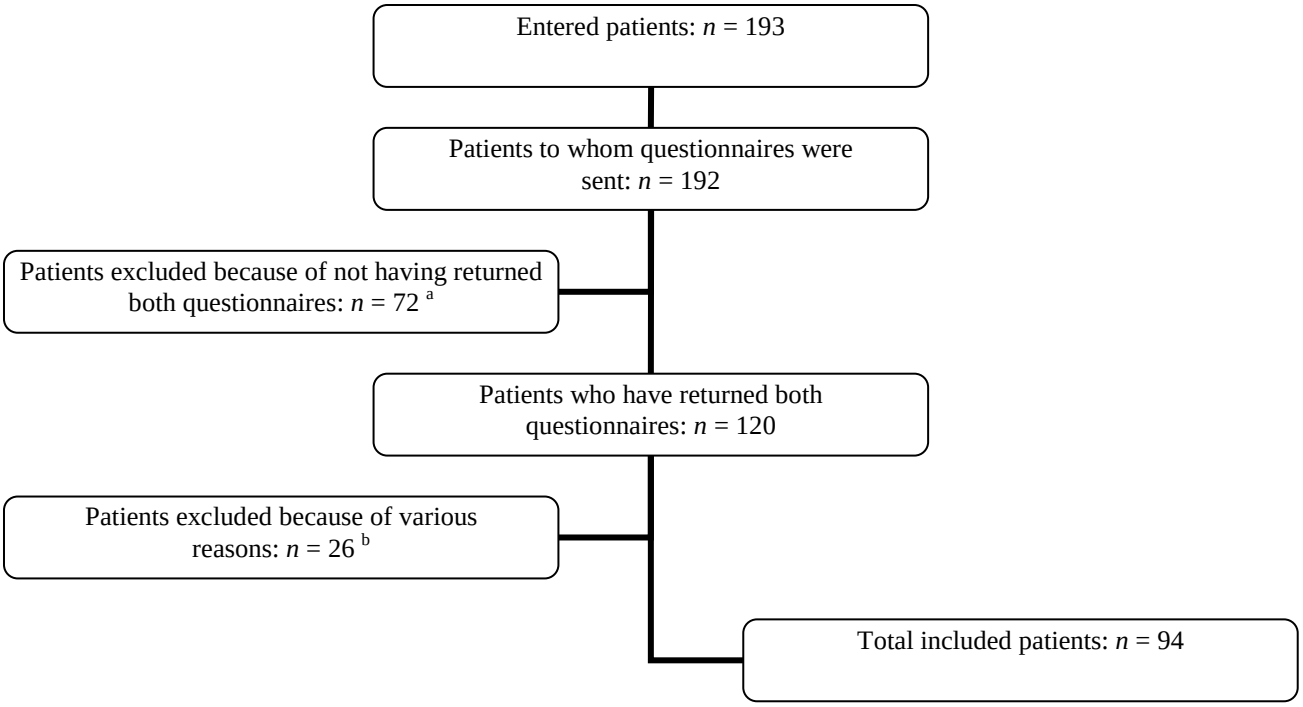

Figure 1. Flow chart of patient inclusion

a
Patients excluded because of not having returned both questionnaires with unknown reason: *n* = 54
Patients excluded because of not having returned both questionnaires with known reason: *n* = 18:
no cluster period or oxygen use: *n* = 15
no correct address and phone number: *n* = 1
no cluster headache: *n* = 2

b
Patients excluded because of:
unknown number of oxygen treated cluster headache attacks: *n* = 3
less than three oxygen treated cluster headache attacks: *n* = 4
no oxygen treatment at all: *n* = 7
no reliable VAS scores: *n* = 1
oxygen treatment in the past: *n* = 9
uncertainty about diagnosis cluster headache: *n* = 1
no cluster headache and oxygen treatment: *n* = 1

Baseline characteristics

Of the ninety-four patients who were included, seventy-five (79.8%) were men. Mean current age was 45.3 (SD 13.0) and median age at onset of CH was 37.0 (IQR 25). Fifty-five (58.5%) patients smoked at the time of inclusion and seventy-seven (81.9%) patients smoked in the past. Of the sixty-one patients who could be reliably classified using the first questionnaire, forty-two (68.9%) had episodic cluster headache (ECH) and nineteen (31.1%) had CCH. Approximately half of patients (54.3%) did not experience interictal headache. The median maximal attack duration without medication was 108 (IQR 120) min in eighty-two patients and of these, seventeen (20.7%) had a maximal attack duration of more than 180 min. Three (3.3%) of ninety-one patients had a maximal attack frequency in the active phase of more than eight per day (range seventy-seven to eighty-four attacks/week in these three

patients) with an average attack frequency of eight or less per day. Following oxygen prescription, the median used oxygen flow rate was 7.0 (IQR 5.0) L/min (range 6.0-25.0 L/min) in ninety-two patients. Ninety patients started using oxygen median 5 (IQR 4) min (range 0-60 min) following headache onset.

Univariate analysis

Comparisons of patient characteristics, headache characteristics and therapies between clear responders (group A) and clear non- plus moderate responders (group B + C) are shown in Tables 2, 3 and 4 respectively. There were no statistical significant differences in patient and headache characteristics. There was one statistical significant difference in therapies.

Relatively more clear responders than clear non- plus moderate responders smoked in the past (90.2% *versus* 71.0%) and this difference approximated statistical significance. There was no difference in the median age at which patients started smoking and the median number of pack years per smoker. In their current active phase relatively more clear responders than clear non- plus moderate responders were able to drink alcoholic beverages (63.4% *versus* 41.9%), but this difference was not statistical significant. There was no difference in the median number of alcoholic beverages, which were drunk per week by these patients.

There was a trend of clear non- plus moderate responders experiencing untreated attacks of longer duration than clear responders. Especially the difference in percentage of patients, who experienced maximal attack durations of more than 180 min, approached statistical significance. There was no difference in the presence of interictal headache. There seemed a second, small trend of clear non- plus moderate responders experiencing a higher attack frequency in active phases than clear responders. There was, however, no difference in ever (*i.e.* before the start of oxygen therapy as attack treatment) and current (*here* following the start of oxygen therapy as attack treatment) use of verapamil and ever use of lithium and methysergide (not shown in Table 4). Statistical significant (p = 0.03) more clear non- plus moderate responders than clear responders had ever used pizotifen (13.8% *versus* 0.0%), but the absolute number of users was small in the group of clear non- plus moderate responders. There was relatively more current triptan use by clear non- plus moderate responders than clear responders (50% *versus* 27.5%), however, the difference was not statistical significant. Relatively more clear responders than clear non- plus moderate responders had ipsilateral rhinorrhoea during attacks (70.0% *versus* 44.8%) and this difference neared statistical significance. However, other related ipsilateral parasympathetic autonomic features such as lacrimation and nasal congestion did not differ. Slightly more clear-non plus moderate responders than clear responders experienced photo- or phonophobia during attacks (67.7% *versus* 48.8%), but again there was no statistical significant difference.

Clear responders and clear non- plus moderate responders used the same median oxygen flow rate of 7 L/min with an IQR of 5 (range 6.0-25.0 and 6.5-25.0 respectively), following headache onset

after a median of 2 respectively 3 min. Despite absent or moderate responses, 35.5% of clear non- plus moderate responders experienced an effect of oxygen in more than half of CH attacks and 63.3% classified their response as good (not shown in Table 4).

There was no difference in an experienced good response (*i.e.* much or total relief of pain) to cold (for example by use of cold packs).

Table 2. Comparison of patient characteristics between clear responders (group A) and clear non- plus moderate responders (group B + C)

Patient characteristics	Clear responders		Clear non- plus moderate responders		Significance (*p*)
		Group total *n*		Group total *n*	
Men, *n* (%)	32 (78.0)	41	26 (83.9)	31	0.77 [a]
Current age, mean (SD)	47.4 (13.1)	41	45.9 (11.2)	31	0.61 [b]
Number of participants currently older than 49, *n* (%)	20 (48.8)	41	13 (41.9)	31	0.74 [c]
Current BMI, median (IQR)	25.3 (5.9)	41	25.5 (5.6)	30	0.22 [d]
Smoking					
Current smoking, *n* (%)	29 (70.7)	41	17 (54.8)	31	0.25 [c]
Past smoking, *n* (%)	37 (90.2)	41	22 (71.0)	31	0.06 [a]
Pack years per smoker, median (IQR)	20 (18)	37	21 (26)	22	0.85 [d]
Age at start smoking, median (IQR)	16.0 (5.0)	37	16.0 (5.6)	22	0.89 [d]
Alcohol consumption					
Current consumers of alcohol, *n* (%)	26 (63.4)	41	13 (41.9)	31	0.12 [c]
Current number of alcoholic consumptions/week per user, median (IQR)	6.5 (7.8)	24	10.0 (7.0)	13	0.51 [d]
Consumers of alcohol in the past, *n* (%)	28 (71.8)	39	20 (66.7)	30	0.85 [c]
History of					
Sleep apnoea, *n* (%)	3 (7.5)	40	3 (10.0)	30	1.00 [a]
Other headache disorder(s), *n* (%)	19 (46.3)	41	12 (40.0)	30	0.77 [c]
Head trauma, *n* (%)	11 (27.5)	40	11 (37.9)	29	0.51 [c]
Positive family history (1st & 2nd degree) for cluster headache, *n* (%)	5 (12.2)	41	4 (12.9)	31	1.00 [a]

[a] Fisher's exact test, [b] Independent samples *t* test, [c] Chi-square test, continuity correction, [d] Mann-Whitney *U* test

Table 3. Comparison of headache characteristics between clear responders (group A) and clear non- plus moderate responders (group B + C)

Headache characteristics	Clear responders		Clear non- plus moderate responders		Significance (*p*)
		Group total *n*		Group total *n*	
Age at onset cluster headache, median (IQR)	37 (25)	40	41 (22)	31	0.63 [a]
Strict unilaterality of cluster headache, *n* (%)	39 (97.5)	40	28 (90.3)	31	0.31 [b]
Attack duration without medication in min					
Minimal, median (IQR)	30 (25)	37	35 (45)	24	0.38 [a]
Average, median (IQR)	60 (60)	38	60 (106)	26	0.19 [a]
Maximal, median (IQR)	90 (124)	38	165 (140)	27	0.18 [a]
Maximal and more than 180 min, *n* (%)	5 (13.2)	38	9 (33.3)	27	0.07 [b]
No interictal headache, *n* (%)	25 (61.0)	41	15 (48.4)	31	0.41 [c]
Accompanying autonomic features					
Conjunctival injection, *n* (%)	31 (77.5)	40	20 (66.7)	30	0.46 [c]
Lacrimation, *n* (%)	36 (87.8)	41	25 (83.3)	30	0.73 [b]
Nasal congestion, *n* (%)	26 (63.4)	41	24 (80.0)	30	0.21 [c]
Rhinorrhoea, *n* (%)	28 (70.0)	40	13 (44.8)	29	0.06 [c]
Miosis, *n* (%)	20 (58.8)	34	13 (54.2)	24	0.93 [c]
Ptosis, *n* (%)	33 (80.5)	41	21 (67.7)	31	0.34 [c]
Accompanying other features					
Restlessness, *n* (%)	37 (90.2)	41	28 (90.3)	31	1.00 [b]
Nausea/vomiting, *n* (%)	8 (19.5)	41	9 (30.0)	30	0.46 [c]
Photo-/phonophobia, *n* (%)	20 (48.8)	41	21 (67.7)	31	0.17 [c]
Attack frequency per week in active phase					
Minimal, median (IQR)	7.0 (7.0)	40	8.8 (9.1)	30	0.90 [a]
Average, median (IQR)	14.0 (21.0)	41	21.0 (15.8)	29	0.29 [a]
Maximal, median (IQR)	21.0 (24.5)	39	28.0 (28.0)	31	0.27 [a]
Pain at fixed times, *n* (%)	21 (51.2)	41	15 (48.4)	31	1.00 [c]
Headache during night time, *n* (%)	37 (90.2)	41	29 (93.5)	31	0.69 [b]
First cluster, *n* (%)	16 (39.0)	41	13 (41.9)	31	1.00 [c]
Chronic cluster headache, *n* (%)	7 (25.0)	28	9 (45.0)	20	0.26 [c]
Episodic cluster headache, *n* (%)	21 (75.0)	28	11 (55.0)	20	0.26 [c]
Average cluster duration in weeks, median (IQR)	4.5 (13.1)	20	8.0 (10.0)	11	0.97 [a]
Cluster frequency per year, median (IQR)	0.50 (1.69)	22	1.25 (2.11)	12	0.61 [a]
Much or serious restriction in activities, *n* (%)	23 (57.5)	40	19 (61.3)	31	0.94 [c]
Much or serious restriction in work, *n* (%)	18 (45.0)	40	21 (67.7)	31	0.10 [c]

[a] Mann-Whitney *U* test, [b] Fisher's exact test, [c] Chi-square test, continuity correction

Table 4. Comparison of therapies between clear responders (group A) and clear non- plus moderate responders (group B + C)

Therapies	Clear responders		Clear non- plus moderate responders		Significance (*p*)
		Group total *n*		Group total *n*	
Therapies before start of oxygen therapy					
Current medication use for other disorders, *n* (%)	21 (51.2)	41	19 (61.3)	31	0.54 [a]
Ever used therapies for cluster headache					
Exposure to cold, *n* (%)	24 (58.5)	41	15 (48.4)	31	0.54 [a]
Good response to cold (much or total relief of pain), *n* (%)	3 (12.5)	24	1 (6.7)	15	1.00 [b]
Triptan(s), *n* (%)	23 (57.5)	40	19 (63.3)	30	0.81 [a]
Good response to triptan(s) (much or total relief of pain), *n* (%)	19 (86.4)	22	12 (70.6)	17	0.26 [b]
Verapamil, *n* (%)	24 (58.5)	41	23 (76.7)	30	0.18 [a]
Good response to verapamil (much or total relief of pain), *n* (%)	10 (45.5)	22	7 (35.0)	20	0.71 [a]
Pizotifen, *n* (%)	0 (0.0)	40	4 (13.8)	29	**0.03** [b]
Good response to pizotifen (much or total relief of pain), *n* (%)	0 (0.0)	0	1 (25.0)	4	-
Following start of first ever oxygen therapy					
Current use of oxygen in L/min, median (IQR)	7.0 (5.0)	39	7.0 (5.0)	31	0.31 [c]
Time between headache onset and oxygen start in min, median (IQR)	2 (4)	40	3 (4)	28	0.76 [c]
VAS score before oxygen use, median (IQR)	9 (2)	41	9 (2)	31	0.78 [c]
Triptan use in same active phase, *n* (%)	11 (27.5)	40	15 (50)	30	0.09 [a]
Verapamil use in same active phase, *n* (%)	26 (63.4)	41	20 (64.5)	31	1.00 [a]

VAS score visual analog scale score of 1-10, with score 10 relating to the worst imaginable pain ever
[a] Chi-square test, continuity correction, [b] Fisher's exact test, [c] Mann-Whitney *U* test

Univariate sub-analysis

In the sub-analysis we compared patient characteristics, headache characteristics and therapies between clear responders (group A) and clear non-responders (group B). This sub-analysis could not confirm a statistical significant difference in ever pizotifen use; one clear non-responder had used pizotifen. Furthermore, the sub-analysis could not reveal a statistical significant difference in one of the characteristics (past smoking; maximal attack duration without medication longer than 180 min; rhinorrhoea), which difference approximated statistical significance in the initial univariate analysis. Significant ($p = 0.047$) more clear non-responders than clear responders reported photo- or phonophobia during headache attacks (78.9% *versus* 48.8%), as shown in Table 5. Furthermore, the

sub-analysis disclosed a statistical significant difference ($p = 0.02$) in triptan use, with more clear non-responders than clear responders using a triptan in the same active phase as the phase in which they had used oxygen for the first time (63.2% *versus* 27.5%), also shown in Table 5. We did not find both differences in the univariate analysis. Again, both clear responders and clear non-responders used the same median oxygen flow rate of 7 L/min with an IQR of 5 and a range of 6.0-25.0 and 6.5-15.0 respectively. A flow rate of more than 15 L/min was used by one clear responder.

Table 5. Sub-analysis. Found significant differences in characteristics and therapies between clear responders (group A) and clear non-responders (group B)

Characteristic / therapy	Clear responders		Clear non-responders		Significance (*p*)
		Group total *n*		Group total *n*	
Photo-/phonophobia, *n* (%)	20 (48.8)	41	15 (78.9)	19	**0.05 (0.047**) [a]
Triptan use in same active phase as first ever oxygen therapy, following start of this first ever oxygen therapy, *n* (%)	11 (27.5)	40	12 (63.2)	19	**0.02** [b]

[a] Fisher's exact test, [b] Chi-square test, continuity correction

Post-hoc analysis

To correct for multiple testing, we used the Bonferroni correction to calculate new thresholds of significance for the variables, which differences were statistical significant in the univariate analysis or univariate sub-analysis. Thresholds for significance were 0.01 for the variable 'ever used pizotifen', 0.02 for the variable 'accompanying photo-/phonophobia' and 0.03 for the variable 'triptan use in same active phase as first ever oxygen therapy, following start of this first ever oxygen therapy'. Using this Bonferroni correction, we could only confirm a statistical significant difference in triptan use.

Discussion

In this prospective cross-sectional correlation study of response to oxygen therapy in ninety-four CH patients, we have studied the factors which differ between clear responders and clear non- plus moderate responders as well as between clear responders and clear non-responders. Clear non- plus moderate responders had ever used pizotifen more often. Clear non-responders more often had accompanying photo- or phonophobia during headache attacks and more often had used a triptan in the same active phase as the phase in which they had used oxygen for the first time ever. Following correction for multiple testing, this study only found a statistical significant difference between clear responders and clear non-responders in triptan use in the active phase in which they had used oxygen for the first time ever.

In the present study clear non- plus moderate responders had ever used pizotifen significantly more often. Pizotifen can be used as preventive treatment of CH and is recommended by the Dutch practice guidelines of chronic recurrent headache without neurological abnormalities as one of the second line preventive treatments for ECH and as third choice preventive treatment for CCH.[19] The percentage and absolute number of ever users of pizotifen in the group of clear non- plus moderate responders were small (13.8 % and four respectively) and the difference was not statistical significant using correction for multiple testing. Based on these marginal notes, we do not believe that past use of the serotonin and histamine inhibitor pizotifen will be associated with a current response to oxygen, not to mention a causal relationship.

Second, in this study clear non-responders significantly more often had accompanying photo- or phonophobia during headache attacks than clear responders (78.9% *versus* 48.8%), when not corrected for multiple testing. None of the clear non-responders fulfilled the ICHD-II criteria for migraine without aura [1] and therefore we do not assume a misdiagnosis of migraine with cranial autonomic symptoms (CAS) in these patients.[20] Migrainous symptoms during headache, such as photo- and phonophobia, were self-reported by up to 91% and 89% of CH patients (with a diagnosis according to the IHS criteria of 1988) respectively.[21] In another study, based on the study of several cohorts and patients seen in practice, 65% of CH patients had photo- or phonophobia with attacks.[22] In all TAC groups photo- and/or phonophobia was often lateralized clinically (54% in CH up to 67% in chronic paroxysmal hemicrania) compared to migraine (8%), a difference which was statistical significant ($p < 0.0001$) when comparing episodic primary TACs with episodic migraine only.[23] We did not ask for lateralisation of photo- and phonophobia. Despite clinical experience, at least during cluster periods there was no quantitative difference between symptomatic and asymptomatic sides in light- and sound-induced discomfort thresholds.[21] This lack of quantitative lateralisation of photo- and phonophobia could suggest a mechanism cluster periods and migraine have in common. As there are, to our knowledge, no quantitative measurements of photo- and phonophobia during CH attacks, clinical lateralisation is not confirmed and therefore cannot contribute to our knowledge of the exact level of action of oxygen. The pathophysiology of photophobia, in particular, has been investigated in recent years. Interestingly, the two identified circuits that mediate photophobia both share parts with the trigemino-autonomic reflex in CH. The first photophobia circuit overlaps at the levels of the SSN, pterygopalatine ganglion, vasculature (ocular), trigeminal nerve and ganglion, trigeminal caudal nucleus, thalamus, and cortex. The second circuit overlaps at the levels of the thalamus and cortex. Furthermore, altered activity of the CGRP receptor causes an increase in light aversion.[24] The photophobia circuits contain locations at which oxygen is presently known to exert its action in CH: the SSN and vasculature (also in relation to CGRP). Non-response to oxygen and presence of photo- and phonophobia could be two expressions of a higher nociceptive sensitivity. In our opinion, it would be incorrect to locate, solely based on theoretical grounds, the level of action of oxygen also in the thalamus and cortex.

Third, in this study clear non-responders significantly more often used a triptan in the same active phase as the phase in which they had used oxygen for the first time ever, even when corrected for multiple testing. This seems logical, as alternative attack treatments will be prescribed in case of non-response to oxygen.

In this prospective study, we could not confirm, at a statistical significant level, the results of our retrospective cross-sectional correlation study, in which the variables 'no smoking history', 'interictal headache' and 'a maximal attack duration of more than 180 min' predicted non-response to oxygen.[11] However, compared to clear responders, again clear non- plus moderate responders in this prospective study (comparable to the group 'non-responders' in the univariate analysis of our retrospective study [11]) had smoked in the past less often and had had a maximal attack duration of more than 180 min more often. Differences in both variables approximated statistical significance in this prospective study. Possibly, a larger study population would have led to significant differences in this present study as well.

Comparable to our retrospective study,[11] we left the group oxygen responders with an increase in attack frequency (group E) out of the analysis, because this oxygen response is not considered beneficial. Patients in group E did not completely fulfil our definition of the rebound effect, which was defined as a more rapid than usual (for the individual patient) recurrent CH attack after complete relief following oxygen therapy, or an increase in the number of attacks per 24 hours (h) while using oxygen therapy as acute attack treatment.[10] In the present study, we have asked only for an increase in attack frequency while using oxygen and just a few patients have been contacted to further elucidate the rebound phenomenon.[11] An increase in attack frequency while using oxygen was reported by four clear non- plus moderate responders as well. As lack of a good oxygen response probably will lead to discontinuation of its use in these patients, this will probably not get attention in daily practice, but still deserves further scientific study.

Although we previously ruled out a misdiagnosis of migraine with CAS in non-responders, who had accompanying photo- and phonophobia during headache attacks, it is of interest to mention that the opposite may be applicable, as a recent case report again described the effectiveness of 100% oxygen as attack treatment in a migraine patient with lateralised CAS.[25] This seems in agreement with the effects of oxygen on the parasympathetic SSN in rats.[13] In our study, however, we could not find a statistical significant difference in the presence of parasympathetic autonomic symptoms between clear responders and clear non- (plus moderate) responders. Interestingly, migraine patients with a smoking history (past and current smoking) of at least 1 serried year were found to have associated autonomic symptoms (not necessarily lateralised) significantly more often than migraine patients without this smoking history.[26] Ever smoking increases the concentration of nicotinic acetylcholine receptors (nACHRs) in the brain stem, which could hypothetically lead to more prominent autonomic symptoms, via vasoactive intestinal polypeptide (VIP) modulation of the receptors.[26] Although not

hypothesised in our retrospective study, in which we found absence of past smoking to be a predictor of non-response to oxygen,[11] these nACHRs could be a focus in future research in oxygen therapy.

One of the weaknesses of this prospective study is the lack of control of the way of oxygen delivery and breathing techniques used. For example, hyperventilation may cause hyperoxia and hypocapnia, both of which induce cerebral vasoconstriction. As all of the ninety-two patients with known oxygen flow rates used at least 6 L/min of continuous flow oxygen, of which 96.7% used at least 7 L/min, most patients should have used an oxygen face mask. However, there are different types of face mask, with and without non-rebreathing system and with various degrees of fitting to the face. The type of oxygen mask in combination with breathing technique used is probably one of the factors that determines oxygen efficacy, as in a recent pilot study all four CCH patients treated with demand valve oxygen with hyperventilation became pain free within 20 min of oxygen use, in contrast to two of three patients treated with continuous flow oxygen.[27] Further study is necessary, but it may be assumed that the type of oxygen delivery system for continuous flow oxygen and the breathing pattern could have been confounding factors in this study.

Another weakness of the present study is the use of questionnaires. To reduce the number of unintentional false answers, we contacted patients by phone to elucidate answers and we left a few questions, which had been interpreted in different ways by different patients, out of statistical analysis.

Conclusion

Clear non- plus moderate responders to oxygen had ever used pizotifen more often. Clear non-responders to oxygen more often had photo- or phonophobia during headache and more often had used triptans in the same active phase as the phase, in which they had used oxygen for the first time. Using correction for multiple testing, we could only confirm a statistical significant difference in triptan use.

In this study, we were unable to locate the level of action of oxygen in the thalamus and cortex or confirm the sites of its action presently known, solely based on current knowledge of photophobia circuits.

We believe that particularly the higher frequency of photo- or phonophobia in clear non-responders to oxygen deserves further study to understand the mechanism of pain reduction by oxygen and CH pathophysiology.

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Chapter 5

Rebound following oxygen therapy in cluster headache

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Abstract

Background. Rapid recurrence of a new cluster headache attack following oxygen treatment was named the ‘rebound effect’ by Kudrow (1981). It has never been studied properly. To study this effect, we defined it as a more rapid than usual (for the individual patient) recurrent cluster headache attack after complete relief following oxygen therapy, or an increase in the number of attacks per 24 hours while using oxygen therapy as acute attack treatment. We reviewed the literature and searched our cluster headache study databases.

Case series. In our eight patients with rebound cluster headache, the effect was experienced following 87.5% of oxygen treated attacks. Duration until the next cluster headache attack was on average 894 minutes shorter and frequency was on average 1.6 cluster headache attacks per day higher than without oxygen therapy.

Conclusion. Although the 1981 trial reported a prevalence of 25%, rebound cluster headache following oxygen therapy is rarely reported nowadays. This may be due to better techniques in oxygen application, the use of higher oxygen flow rates or underreporting. The few literature data and data on our eight patients did not provide clues about the mechanism of the rebound effect. Further study, applying the proposed definition, seems useful.

Introduction

Oxygen has been used to treat cluster headache (CH) attacks since 1952.[1] Not much is known about its mechanism of action and why it provides a successful or significant headache relief in 75-82% of the patients using a flow rate of 6-8 litre/minute (L/min).[2] Therefore, we carried out a retrospective cross-sectional correlation study,[2] in which we assessed the characteristics that differentiate between CH patients who respond to oxygen and those who do not.[2] Currently, this subject is being investigated further in a prospective study.

One of the observations from these studies was that some patients reported a complete response to oxygen within 15 minutes (min), but noticed rapid recurrence of a new attack, giving the impression that oxygen only postpones the attack. Such attacks return sooner than attacks not treated at all. The phenomenon was described in Kudrow's 1981 oxygen trial and called 'rebound headache'.[3] Given that the rebound effect of oxygen therapy in CH patients has never been studied adequately, we studied the phenomenon by doing a literature search and describing the patients we observed. We therefore defined the rebound effect as a more rapid than usual (for the individual patient) recurrent CH attack after complete relief following oxygen therapy, or an increase in the number of attacks per 24 hours (h) while using oxygen therapy as acute attack treatment.

Case series

We describe four of 115 (3.5%) patients from our retrospective study,[2] three of forty-three (7.0%) patients from our current prospective study and one outpatient, all of whom reported a complete relief of a CH attack following oxygen therapy, followed by a more rapid recurrence of CH attacks or an increase in the attack frequency. All patients used oxygen only as acute CH attack treatment. One hundred percent oxygen was applied using a non-rebreathing face mask. Rebound CH was reported spontaneously in the retrospective study. In our current prospective study, we specifically asked about a change in attack frequency after start of oxygen therapy. Patients 4 and 8 (Tables 1 and 2) spontaneously reported a more rapid recurrent CH attack, although attack frequency and time between the initial and rebound CH attack were not reported. The outpatient said that 'In my opinion, oxygen seems to postpone about 50% of the CH attacks, finally leading to a shorter period between the attacks which increase in both duration and severity'. Patient and headache characteristics and effectiveness of oxygen therapy are summarized in Tables 1 and 2. Patients could clearly make a distinction between a CH attack and interictal headache. On average, rebound CH was experienced in 87.5% of oxygen treated CH attacks (range 50–100%); the mean duration until the next CH attack was 39 min (range 0–120) when using oxygen instead of 933 min (range 165–1440) without using oxygen; the mean frequency was 4.1 CH attacks/day (range 2-8) when using oxygen instead of 2.5 CH attacks/day (range 0.5-7) without using oxygen.

Discussion

A PubMed search did not provide additional information about the rebound effect, except that most of those referring to the phenomenon quoted Kudrow.[3] Searching the books *The Headaches*[4] and *Cluster Headache Syndrome*[5] did not result in additional references.

Kudrow was the first to report the rebound effect in 1981.[3] Twenty-five percent of the patients, who initially responded well to 100% oxygen administered through a face mask at a flow rate of 7 L/min for 15 min, reported rebound CH.[3] Mathew experienced that a number of patients responding to oxygen reported having recurrent headache within a short time, for which repeated oxygen administration was required.[6] Torelli and Manzoni described the rebound effect as a 'reappearance of pain after 1-2 hours of oxygen inhalation'.[7] It is not clear for what reason they chose this time limit.

Using our definition, we found seven patients in our combined study group of 158 patients (4.4%) who reported the rebound phenomenon, which is much less than the 25% reported by Kudrow.[3] Possibly, the phenomenon occurs more rarely because of better techniques in applying oxygen or because of the tendency to increase the oxygen flow rate. Another explanation may be that patients are rarely interviewed about the phenomenon, as might have been the case in our retrospective study.

Recurrence of CH attacks has been reported in long-term[8] as well as short-term[9] treatment with subcutaneous sumatriptan. In the latter, sumatriptan provided 'relief' (in one patient) or 'complete relief' (in five patients) within 5 min following subcutaneous administration, but the CH attack frequency increased to 150-1100% of its original frequency. The increased attack frequency occurred already after 48 h in one patient and after the second dose in another. The attack frequency also showed a linear relationship with the number of sumatriptan injections per 24 h. Owing to the high number of CH attacks, sumatriptan became quickly overused. Rossi *et al.* state that the increased CH attack frequency suggests a drug-induced event, probably because of the short-lasting effect of subcutaneous sumatriptan.[9] The rebound effect of oxygen therapy was also experienced immediately by three of our patients, and therefore seems to occur as early as in sumatriptan use. Six of our eight patients had used triptans at some point, and none of them experienced rebound CH following their use. It is not known whether patients experiencing rebound following use of subcutaneous sumatriptan are more prone to rebound following oxygen therapy.

Taken together, these preliminary data on the rebound effect following sumatriptan and oxygen use in CH patients suggest an effect of specific substances with a short half-life. Because of the immediate development of rebound CH after the first use of oxygen therapy in three patients, rebound CH is not (only) the result of medication overuse or tachyphylaxis, which would be more likely after intake over longer periods.

As mentioned earlier, we hypothesize that oxygen flow rates may play a part in the effectiveness of oxygen therapy, as four out of the six patients with known oxygen flow rates who experienced rebound CH used an oxygen flow rate of 7.0 L/min or less. The effectiveness of use of

high oxygen flow rates (12-15 L/min) was recently reported by Rozen [10] and Cohen *et al.*[11] Cohen *et al.*'s trial did not report a rebound effect; the investigators [11] asked the patients to report the time between achievement of a pain free state and the next attack, but only few datapoints were obtained, for which reason they did not study it further (personal communication by P. Goadsby, 25 August, 2010). Further research on this subject is obviously necessary.

Conclusion

Rebound CH following oxygen therapy has rarely been reported in the literature since it was mentioned to occur in 25% of the patients in Kudrow's 1981 trial.[3] The phenomenon may have occurred more rarely since, because of better techniques in applying oxygen or because of the tendency to increase the oxygen flow rate. Another explanation may be underreporting. To identify patients with rebound CH following oxygen therapy, we defined this rebound effect as a more rapid than usual (for the individual patient) recurrent CH attack after complete relief following oxygen therapy, or an increase in the number of attacks per 24 h while using oxygen therapy as acute attack treatment. We believe rebound CH following oxygen therapy deserves more attention and should be asked about when treating CH patients with oxygen. Given that little is still known about the origin and the development of the rebound effect, more prospective research on this subject is obviously necessary, in particular on a possible relationship between oxygen flow rates and rebound CH.

Table 1. Patient characteristics

	Retrospective study				Prospective study			Outpatient
Patient	1	2	3	4	5	6	7	8
Gender, age (yrs)	M, 39	F, 47	M, 48	M, 24	F, 26	M, 32	M, 23	M, 61
Age at onset of CH (yrs)	34	30	42	18	25	25	22	52
Type of CH	E	E	C	C	C	E	E	E
Duration of cluster period*	15 weeks	3 weeks	Not known	Not known	1.5 yrs	4 weeks	8 weeks	13 weeks
Interictal headache	+	+	+	+	-	+	+	-
Past medication (before O_2 therapy)	Triptans	Verapamil, triptans (simultaneous use with O_2 is not clear)	Triptans, acetaminophen (simultaneous use with O_2 is not clear)	Verapamil, NSAIDs (simultaneous use with O_2 is not clear)	-	-	Metoprolol, sodiumvalproate, naproxen, amitriptyline, triptans	Triptans
Current medication (during O_2 therapy)	Verapamil	Verapamil, triptans (simultaneous use with O_2 is not clear)	Verapamil	Verapamil, NSAIDs (simultaneous use with O_2 is not clear)	Verapamil	Verapamil, triptans, NSAIDs	Verapamil	Verapamil
History of other headache disorders	-	TTH	+†	-	MO	-	+‡	-

CH: cluster headache, E: episodic, C: chronic, yrs: years, M: male, F: female, O_2: oxygen, TTH: tension type headache, MO: migraine without aura

* 'Duration of cluster period' is the mean duration of past cluster periods of patients 1 and 2 and current duration of the cluster period in patients 5, 6, 7 and 8.

† Type of headache disorder unknown.

‡ Chronic headache; no medication overuse headache.

Table 2. Cluster headache characteristics (including baseline parameters and with oxygen therapy)

	Retrospective study				Prospective study			Outpatient
Patient	1	2	3	4	5	6	7	8
Average number of CH attacks/day without O_2 therapy	7	1	1	2	4	1	0.5 - 1	3
Average number of CH attacks/day with O_2 therapy	8[‡]	2	6	[*]	4[‡]	3-4[‡]	2-3	3
Average duration of CH attacks without O_2 therapy (min)	45	450[†]	83	60	23	120	120	180
Average duration until complete relief of CH after start O_2 therapy (min)	7.0	10.0	20.0	1.5	5.0	15.0	12.0	10.0
Average duration until new CH attack without O_2 therapy (h)	2.75	24	Not known	[*]	3	24	24	[*]
Average duration until new CH attack after initial attack for which O_2 was used (h)	0.50	Immediately	Not known	[*]	0.38	0.75	2.0	0.25
Use of O_2 therapy	5 yrs	3 yrs	Not known	Not known	4 weeks	8 weeks	10 weeks	7 yrs
Frequency of O_2 therapy (times/day), (days/week)	3-4/day, 7days/week[‡]	2/day, Not known	Not known	Not known	2/day, 5days/week[‡]	2/day, 7days/week[‡]	3/day, 7days/week	3/day, 7days/week
O_2 flow rate (L/min)	6.0	Not known	7.0	Not known	7.0	7.0	12.0	12.0
Time between first use of O_2 therapy and developing rebound CH	Immediately	2.5 yrs	9 weeks	10-15 times O_2 therapy	Immediately	1 week	9 weeks	Immediately
Percentage of rebound attacks	100%[¶]	100%[¶]	100%[¶]	100%[¶]	50%[¶]	100%[¶]	100%[¶]	50%[¶]

CH: cluster headache, O2: oxygen, yrs: years.

[*] Patients 4 and 8 spontaneously reported a rapid recurrent CH attack after using oxygen therapy for the initial CH attack. Attack frequency and time between initial and rebound CH attack were not reported.

[†] Patients did not necessarily have to fulfill the criteria of a maximum attack duration of 3 h, as Van Vliet *et al.* state that this upper limit of a CH attack may be too strict.[12]

[‡] The total number of CH attacks in a day on which a patient used oxygen. The frequency of oxygen therapy can be less, because oxygen is not used during every CH attack. Patient 6 used triptans to treat some of the CH attacks.

[¶] All patients experienced rebound CH during each cluster.

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Chapter 6

Nociception specific supraorbital nerve stimulation may prevent cluster headache attacks: serendipity in a blink reflex study

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Abstract

Background. In cluster headache, neuromodulation is offered when patients are refractory to pharmacological prophylaxis. Non-invasive peripheral neuromodulatory approaches are of interest. We will focus on these and particularly on nociception specific, transcutaneous supraorbital nerve stimulation.

Methods. In a study using the nociception specific blink reflex, we made a serendipitous discovery, notably the potential prophylactic effect of bilateral, time contingent, nociception specific, transcutaneous stimulation of the supraorbital nerve.

Results. We report on a case series of seven cluster headache patients, in whom attacks seemed to disappear during repeated stimulation of the supraorbital nerves. Three patients stopped experiencing attacks since study participation.

Conclusions. Bilateral, time contingent, nociception specific, transcutaneous supraorbital nerve stimulation may have a prophylactic effect in episodic and chronic cluster headache. Given its limited side effects and its non-invasive nature further studies to investigate this potential peripheral neuromodulatory approach for both episodic and chronic cluster headache are warranted.

Introduction

When cluster headache (CH) patients are refractory to or do not tolerate pharmacological prophylaxis, peripheral nerve blocks may be effective, but attacks may recur within weeks.[1] The next line of treatment comprises neuromodulation and peripheral as well as central approaches are available. Deep brain stimulation of the posterior hypothalamus,[2] however, may bring on even fatal side effects. Less invasive methods are being studied [3] and occipital nerve stimulation is considered the first-line neuromodulatory approach in refractory chronic cluster headache (CCH), although randomized controlled trials are still awaited for.[4, 5] Because even peripheral invasive neuromodulatory approaches carry a certain risk of device- and surgery-related side effects, non-invasive peripheral neuromodulatory approaches are of particular interest.[4]

Study of the blink reflex is of interest in CH. A concentric planar stimulating electrode with a central cathode and external anode ring selectively stimulates superficial nociceptive A-delta fibres of the supraorbital nerve in the nociception specific blink reflex.[6] In order to further unravel CH pathophysiology, we are investigating the effect of oxygen on medullary interneurons. The study uses a repeated measures design, in which the nociception specific blink reflex is measured every 2 hours (h) before a spontaneous attack, shortly after onset of an attack and 12-15 minutes (min) after start of oxygen treatment. At present, eight patients have enrolled and none of them experienced a spontaneous attack during the clinical study time, reason to report on this series of patients.

Methods

Study population

Patients diagnosed by their neurologist with active CH according to the International Classification of Headache Disorders, second edition (ICHD-II) criteria [7] were included. Patients were excluded in the case of secondary CH, other headache diagnoses or painful conditions, pregnancy or lactation, intolerability of the oxygen face mask and incapacitation to understand and sign for informed consent. Chronic obstructive pulmonary disease and previous thermolesion of the sphenopalatine ganglion were among the relative exclusion criteria. Patients were not allowed to use nitroglycerin, subcutaneous sumatriptan and alcohol in the preceding 2.5, 12 and 24 h respectively and other triptans in the preceding 6 days. Dosages of prophylactic medication were not allowed to be changed in the preceding 2 weeks.

Eligible patients were scheduled for study participation when the chance of occurrence of a spontaneous CH attack was expected to be ‘moderate’ to ‘high’ on that single day in the afternoon or evening (and one night), based on the individual patient’s attack frequency and pattern during previous days and weeks.

Time contingent, nociception specific blink reflex

The supraorbital nerves were electrically and separately stimulated with a 200 pulse per second (pps) train of three 0.5 ms pulses by the special concentric planar stimulating electrode with central cathode and external anode ring,[6] placed on the skin 10 mm cranial of the supraorbital notch on both the affected and non-affected side. The current intensity was adjusted with increasing 0.3 mA steps, delivered at unpredictable intervals, until 2.1 mA (once 2.4 mA), until 1.2 times the intensity of acquired stable R2 responses or until the patient's tolerance limit was reached. Four well-displayed nociception specific blink reflexes were obtained for each side (using the stimulation sequence two at the affected side – four at the non-affected side – two at the affected side), with different intervals of at least 15 seconds to minimize habituation. To exclude diurnal variance, the nociception specific blink reflex without oxygen treatment was elicited every 2 h before the expected occurrence of a spontaneous attack. As a control, the nociception specific blink reflex was measured once outside an attack during 4 min of inhalation of 100% oxygen with a flow rate of 12 litre/min (L/min) using a non-rebreathing face mask.

Questionnaires

Before study participation, patients filled in a questionnaire to double-check the diagnosis and preceding medication use.

At variable times following study participation, we contacted the patients to inquire retrospectively more specifically about medication use and attack frequency and pattern in the week before and following study participation. A diary was kept by two patients in the week before and three patients in the week following study participation.

Ethics

All patients gave written informed consent for participation in the original study, which was approved by the local ethics committee.

Results

At present, eight of targeted twenty CH patients have participated in the study. Despite a double-check of the neurologist's ICHD-II diagnosis of CH,[7] we questioned the diagnosis of one patient during follow-up. We therefore excluded this patient and present the characteristics of seven patients (Table 1; Figures 1-2).

Despite questioning on exclusion criteria and instructions on medication intake beforehand, four patients satisfied at least one exclusion criterion at time of study participation. We chose for continued study participation with complete mention of the satisfied exclusion criteria. All patients located their pain at least in the first trigeminal division.

The pinprick-like pain of the nociception specific stimulation was tolerated by all patients, although in one patient (no. 2) a low current of 0.9 mA had to be used to retain tolerability. Patients underwent a median of six stimulation sequences and, except for one patient, who underwent seven stimulation sequences, the first, third and higher numbered sequences were given at intervals of 2 h. None of the patients experienced a spontaneous attack during the clinical study time of median 8.4 h.

The chance of occurrence of an attack during study time could be considered ‘high’ in patients no. 3-5 (Figure 2). However, patient no. 5 had a dose increase of verapamil 2 days before study participation.

The fact that patients no. 2, 3 and 7 completely stopped experiencing CH attacks since study participation was unexpected and of even more interest. Patients no. 2 and 3 were studied while they were 6 and 8.5 months in their first cluster and their sustained attack freedom lasted for at least 133 and 128 days (*i.e.* time until retrospective inquiring) respectively. Patient no. 7 had CCH and was retrospectively questioned only 13 days following study participation. He was experiencing his longest time of attack freedom since onset of CCH 5 years before. In contrast to these striking frequency decreases, one CCH patient (no. 4) described an increase in attack frequency in the week following study participation. This increase, however, was not sustained, as this patient experienced 6 days of attack freedom 3 months following study participation. We have no data of the period in between.

Table 1. Patient and cluster headache characteristics

Patient number	Gender	ICHD-II diagnosis at study participation	Estimated time in cluster / of CCH at study participation (months)	Age at study participation	Unforeseen satisfaction of exclusion criterion/criteria	Known secondary origin of blink reflex abnormalities	Relevant comorbidities	VAS score of interictal pain at start of study participation	Time following study participation (days) [a]	Treatment for CH in week preceding study participation	Changes made in pharmacological treatment for CH in week following study participation	Estimated maximum time between CH attacks in week before study participation (hours)	Occurrence of CH attack free days in cluster/CCH in year before study participation
1	M	ECH	6	43	no	no	pneumothorax	2 (no indometacin tried)	150	oxygen; verapamil 240 mg b.i.d.	yes: increase of daily dose of verapamil 2 days following study participation	24	yes (seldom)
2	M	first	6	24	yes: no use of verapamil in 24 hours before study participation	no	ADHD marijuana abuse	1 (indometacin 75 mg od tried)	133	sumatriptan sc?; oxygen; verapamil 120 mg t.i.d.	yes: no oxygen use	uncertain	no
3	M	first	8.5	67	no	no	TIA CEA	0	128	oxygen; verapamil 120 mg b.i.d.	yes: no oxygen use	20-22	yes
4	M	CCH	~60	40	no	no		0	140	oxygen	no	uncertain	no
5	M	ECH	1.7	69	yes: 120 mg increase of daily dose of verapamil in 2 days before study participation	no	DM	3 (no indometacin tried)	61	sumatriptan sc; oxygen; verapamil 240 mg od + 360 mg od	no	12	no
6	M	ECH	0.7	45	yes: one glass of alcohol 16 hours before study participation	no		1 (no indometacin tried)	54	sumatriptan tab [b]	no	> 117	yes
7	M	CCH	~60	63	yes: COPD, however with no problems during oxygen therapy [c]; two radio-frequency treatments of sphenopalatine ganglion left	no	myocardial infarction	2 (no indomethacin tried)	13	oxygen; verapamil 80 mg q.d.s.; prednisone	yes: no oxygen use	uncertain	yes [d]
Total group	100% M	~43% ECH ~29% first ~29% CCH	6 (median)	50 (mean)	~43% no ~57% yes	100% no		1.3 (mean)	128 (median)		~43% no ~57% yes	22.5 (median)	~43% no ~57% yes

CCH: chronic cluster headache; CH: cluster headache; ECH: episodic cluster headache; first: first cluster; ADHD: attention deficit hyperactivity disorder; TIA: transient ischemic attack; CEA: carotid endarterectomy; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; M: man; sc: subcutaneous; od: once daily; b.i.d.: twice daily; t.i.d.: three times a day; q.d.s.: four times a day; tab: tablet

[a] All retrospective answers presented in this table were given by the patients at given number of days following study participation

[b] The patient has not taken sumatriptan tablets in the 6 days before study participation, according to the study protocol

[c] The patient uses oxygen at a flow rate of 12 L/min during 15 min as CH attack treatment

[d] The patient had a maximal period of CH attack freedom in 5 years before study participation of 1 week

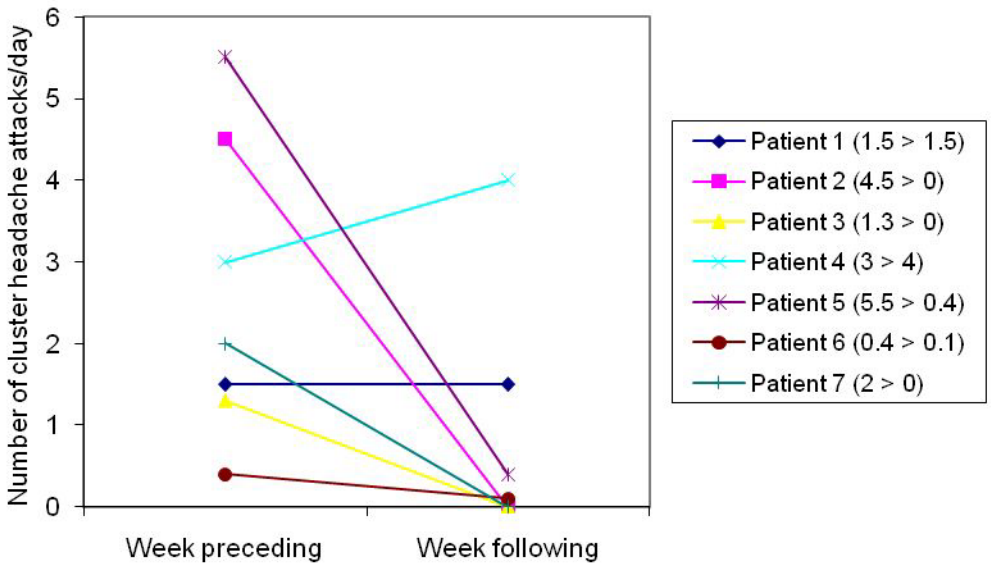

Figure 1. Estimated mean number of cluster headache atacks/day in week preceding and following study participation

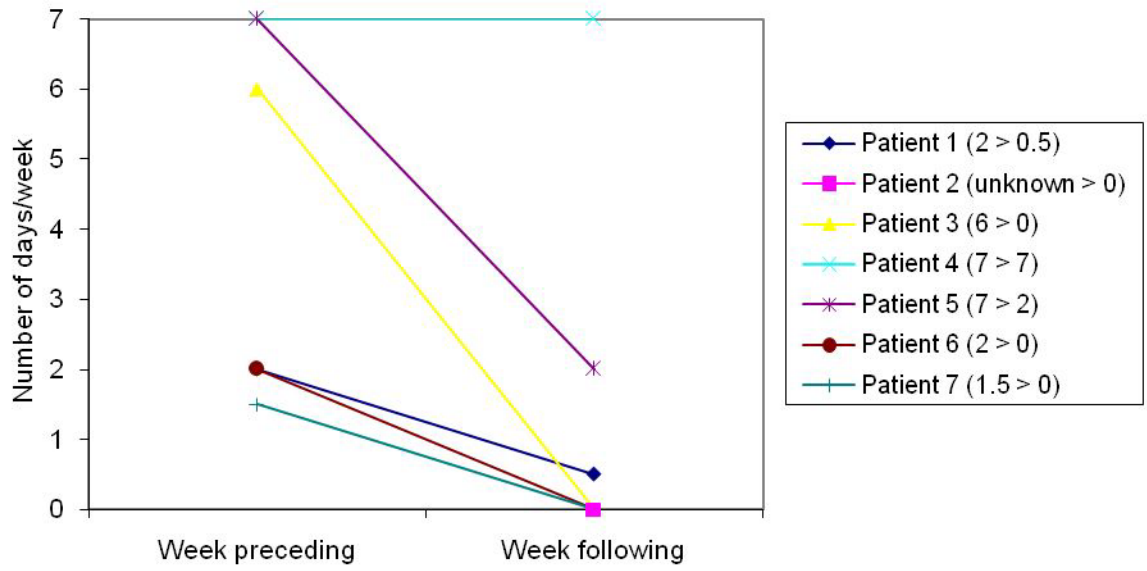

Figure 2. Estimated number of days/week in which the patient experienced a cluster headache attack in afternoon/evening (for patient no. 3: at night)

Discussion

In this study on CH pathophysiology, we may have found a serendipitous discovery that is of importance for future prophylactic treatment studies. All our seven CH patients did not experience any attack during study participation using 2-hourly, nociception specific, transcutaneous stimulation (NSTS) sequences on the bilateral supraorbital nerves to elicit nociception specific blink reflexes. Furthermore, three of seven CH patients have not experienced any attack following study participation.

Non-invasive supraorbital nerve stimulation

The supraorbital nerve can easily be stimulated in a *non-invasive* way, transcutaneously. In a recent double-blind trial (PREMICE) in migraine patients, bilateral, daily transcutaneous stimulation of the supraorbital and supratrochlear nerves was proven effective. No adverse or side effects were reported.[8] A prophylactic effect of punctual transcutaneous electrical nerve stimulation in migraine patients, after more than 6 months, was shown in 1988, although methodological concerns may be raised in that study.[9]

NSTS as possible prophylactic therapy offers advantages over invasive stimulation and pharmacological therapy. First, side effects are few. It is known to produce a pinprick-like pain at intensities of more than 0.6 mA.[6] Furthermore, there is a possible counter effect of an increase in CH attack frequency, as experienced by patient no. 4. A second advantage of NSTS is the non-invasiveness of the procedure. It gets around the known side effects of invasive peripheral neuromodulatory approaches, which include electrode migration, local infections and depletion of the implantable battery.[4] Furthermore, as there are no fixed electrodes, stimulation can be easily applied on both sides and for a certain period of time, preventing the problem of side shift and allowing episodic cluster headache (ECH) patients to be treated by neuromodulation, respectively.

Neurostimulation and cluster headache pathophysiology

At present, little is known about CH pathophysiology and mechanism of action of neurostimulation. Peripheral nerve stimulation is traditionally thought to modulate the intrinsic electrical, afferent impulses travelling to the brainstem and higher. The ‘gate-control theory’ of Melzack and Wall deals with the influence of a competition between nociceptive and innocuous signals on second-order neurons,[10, 11] the latter signals transmitted by A-beta fibres. One may question the applicability of this theory to NSTS of the supraorbital nerve, in which nociception specific stimulation of trigeminal A-delta afferents seems to suppress the transmission of the other nociceptive (*i.e.* headache) signal on a segmental level. Furthermore, mediation in the analgesic effect of descending pain inhibitory pathways through stimulation of ascending tracts by peripheral nerve stimulation has been suggested.[11] In addition to a central influence, Reed and colleagues speculated on a possible relationship with the only partial convergence of trigeminal and occipital neurons on the unilateral trigeminocervical

complex.[12] In that way, direct stimulation of the terminal branches of the trigeminal nerve in particular could play an additional role.

It is obvious that our findings need to be interpreted carefully and that further studies are required. There are several limitations in our present case series, including the absence of a control group; some violations to the study protocol; the heterogeneity in clinical study time, stimulation characteristics, group of patients and data collection; and the small sample size.

In conclusion, bilateral, time contingent, nociception specific, transcutaneous supraorbital nerve stimulation could have a prophylactic effect in ECH and CCH. The suggested effect emerged as serendipity in a study using the nociception specific blink reflex to investigate the effect of oxygen treatment on medullary interneurons in CH. Given its limited side effects and its non-invasive nature, further studies are required.

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Chapter 7

High-flow oxygen therapy in cluster headache patients has no significant effect on nociception specific blink reflex parameters: a pilot study

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Abstract

Background. The exact pathophysiology of cluster headache is unclear. We examined the influence of interneurons on the trigemino-facial reflex arch and the effect of oxygen, by using the nociception specific blink reflex parameters.

Findings. There is no significant effect of oxygen, immediately and over time, on the nociception specific blink reflex parameters in ten male patients during the active phase of cluster headache, outside attacks. Also, there is no significant difference between the symptomatic and asymptomatic side. None of the subjects experienced a cluster headache attack during study participation. We therefore present the collected data as reference values of nociception specific trigeminal stimulation and the effect of oxygen on nociception specific blink reflex parameters.

Conclusion. The nociception specific blink reflex seems not a suitable instrument for exploring the pathophysiology of cluster headache.

Introduction

The exact pathophysiology of cluster headache (CH) is unclear. Previous studies have shown that 100% oxygen therapy is a notable CH attack reliever.[1] Exactly how oxygen exerts its pain reducing effect in patients with CH is uncertain, but it is shown to directly or indirectly cause vasoconstriction. Indirect vasoconstriction can be the result of a possible action on the parasympathetic outflow from the superior salivatory nucleus (SSN), as is shown in rats.[2]

The blink reflex (BR) is a brainstem reflex, elicited through stimulation of the supraorbital nerve, derived from the first branch of the trigeminal nerve, resulting in a bilateral blink reaction of the eyelids through the facial nerve. The BR is composed of an early pontine response (R1), and a late medullary response (R2).[3] R1 is oligosynaptic, ipsilateral and not clinically visible, whereas R2 is polysynaptic, bilateral and clinically observable.[4] A nociception specific blink reflex (nBR) can be elicited by transcutaneously selectively stimulating superficial nociceptive A-delta fibers of the supraorbital nerve with a concentric planar stimulating electrode. The response consists of only a bilateral R2. Using the nBR, the function of the afferent trigeminal and efferent facial nerves and their central connections can be assessed.[3]

We wanted to examine the influence of interneurons on the trigemino-facial reflex arch and the effect of high-flow (12 litre/minute (L/min)) oxygen by using the nBR and its parameters. However, none of the subjects experienced a CH attack during study participation, despite the fact that all of the subjects were in a cluster period at the time. This was possibly due to a preventive effect of nociception specific trigeminal stimulation on CH attacks.[5] We therefore present the data as reference values of the nBR parameters in patients in a cluster period outside a CH attack and the effect of high-flow oxygen inhalation.

Methods

Information concerning study population, in- and exclusion, equipment and questionnaires was already described in a previous publication.[5] The study was approved by the local ethics committee. All patients gave written informed consent. The study terminated early because none of the patients experienced a CH attack during clinical study time. One patient was excluded because the diagnosis of CH was questioned following study participation. CH patients were not compared to healthy controls; the baseline measurement was considered a control.

We elicited nBRs in eleven patients using Synergy EMG equipment (Natus Neurology). For stimulation we used a concentric planar electrode with central cathode and external anode ring (K2 concentric ring stimulating electrode, 1.5 mm; Inomed, Emmendingen, Germany). Disposable silver/silver chloride electrodes were placed over the orbicularis oculi muscles, just lateral of the mid-pupillary line (active) and near the lateral canthus (reference). The ground electrode was placed on the chin. The supraorbital nerve was stimulated 10 mm cranial of the supraorbital notch with a 200 pulse per second (pps) train of three 0.5 ms pulses. The current intensity was increased stepwise by 0.3 mA,

with regard to the tolerance limit of the patient, up to 20% above the level that acquired stable R2 responses to assure supramaximal stimulation, with a maximum of 2.1 mA (once 2.4 mA). The stimuli were delivered at unpredictable intervals of at least 15 seconds to minimize habituation. Both the symptomatic and the asymptomatic side were stimulated until we had obtained four blink reflexes on each side (here referred to as one measurement). In each subject, the R2 responses were elicited at at least the five time points: before oxygen inhalation, during oxygen inhalation and every 2 hours (h) thereafter up until 6 h after oxygen inhalation. It was originally planned to continue until a spontaneous CH attack occurred, but this did not happen.

We analyzed the measurements before, during and 6 h after oxygen inhalation. All responses were evaluated by two researchers (DH and MH). For each stimulation site and time we calculated the shortest latency, amplitude, duration and area of the R2 response using Synergy Reader version 20.1.0.100 (Natus Neurology).

Statistical analysis

We performed the analyses using IBM SPSS statistics version 21. Variables were tested for normal distribution (Shapiro-Wilk). We calculated mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate. Differences of mean were tested with a paired samples t-test. Differences of median were tested using Wilcoxon signed-rank test. Significance levels were adjusted for multiple testing by Bonferroni correction ($p < 0.0025$).

Results

Ten CH patients were included. All CH patients were men. Mean age was 45.7 (range 24-69). Mean BMI was 24.0 (range 20.5 – 36.0). Three patients had episodic cluster headache (ECH), five patients had chronic cluster headache (CCH) and two patients were in their first cluster. Six patients experienced attacks on the left side, four on the right. Eight patients were current smokers.

Table 1 shows the nBR parameters of the symptomatic and asymptomatic side after both ipsilateral and contralateral stimulation, and before and after oxygen inhalation ($n = 10$). There is no significant difference in the nBR parameters before and during oxygen inhalation. There were also no differences in baseline parameters when the symptomatic side was compared to the asymptomatic side. We then studied the difference between the measurements before oxygen inhalation and 6 h after oxygen inhalation ($n = 9$; the measurement in one subject was rejected because it was impossible to elicit R2 responses after 6 h). This difference was not significant either and we considered the values 6 h after oxygen inhalation as a baseline again.

Table 1. Nociception specific blink reflex variables at baseline and during high flow oxygen inhalation (12 L/min)

Nociception specific blink reflex variable	Baseline mean (SD) *	During high flow oxygen inhalation mean (SD) *	*p* value
R2 latency, symptomatic side (ms)			
ipsilateral stimulation	44.95 (5.65)	47.09 (6.29)	0.225
contralateral stimulation	48.75 (6.53)	50.56 (6.03)	0.392
Shortest R2 latency, symptomatic side (ms)			
ipsilateral stimulation	39.05 (6.55)	43.37 (6.19)	0.025
contralateral stimulation	44.12 (6.69)	44.65 (4.16)	0.789
R2 amplitude, symptomatic side (mV)			
ipsilateral stimulation	0.27 (0.10)	0.25 (0.08)	0.387
contralateral stimulation	0.19 (0.07)	0.17 (0.07)	0.235
R2 duration, symptomatic side (ms)			
ipsilateral stimulation	52.63 (14.39)	50.36 (13.65)	0.263
contralateral stimulation	47.74 (19.17)	45.74 (14.27)	0.381
R2 area, symptomatic side (mVms)			
ipsilateral stimulation	2.28 (1.03)	2.04 (0.94)	0.202
contralateral stimulation	1.57 (0.78)	1.25 (0.47)	0.132
R2 latency, asymptomatic side (ms)			
ipsilateral stimulation	47.62 (10.60)	46.01 (8.96)	0.223
contralateral stimulation	49.93 (9.44)	48.85 (7.51)	0.418
Shortest R2 latency, asymptomatic side (ms)			
ipsilateral stimulation	42.92 (10.73)	40.18 (9.40)	0.086
contralateral stimulation	44.17 (10.21)	42.58 (8.51)	0.484
R2 amplitude, asymptomatic side (mV)			
ipsilateral stimulation	0.32 (0.15)	0.27 (0.11)	0.100
contralateral stimulation	0.19 (0.09)	0.16 (0.09)	0.174
R2 duration, asymptomatic side (ms)			
ipsilateral stimulation	49.29 (19.30)	53.80 (16.54)	0.216
contralateral stimulation	47.97 (18.11)	49.50 (16.53)	0.394
R2 area, asymptomatic side (mVms)			
ipsilateral stimulation	2.40 (1.13)	2.26 (0.86)	0.544
contralateral stimulation	1.61 (0.82)	1.32 (0.64)	0.068

* All variables were normally distributed.

Discussion

In this study on the pathophysiology of CH using 2-hourly transcutaneous stimulation sequences on the supraorbital nerves to elicit the nBR, none of the included patients did experience a CH attack during study participation. This may be an important serendipitous discovery for future prophylactic treatment studies, which we have discussed before.[5]

Based on the nBR parameters there is no significant effect of oxygen, immediately and over time. There is also no significant difference between the symptomatic and asymptomatic side of the nBR parameters during the active phase of CH, but outside CH attacks. The stringent correction for multiple testing poses a risk for false negative results. Using no correction, however, none of the results (except for the 'ipsilateral shortest R2 latency symptomatic side during oxygen administration' and 'contralateral area asymptomatic side after 6 h') would have been significant.

It would be interesting to observe what will happen at brainstem level *during* CH attacks in humans. However, if noninvasive nociception specific supraorbital nerve stimulation (SNS) indeed is confirmed to act in a prophylactic way in CH, it may be difficult to measure nBR parameters during a CH attack.

The nBR was first studied in healthy subjects using a custom built concentric planar stimulating electrode allowing only the nociception specific A-delta fibers to be stimulated.[3] The nBR was further characterized in 104 healthy volunteers without any history of headache. Mean R2 onset latencies were 44.7 ms ipsilateral and 45.4 ms contralateral.[6] We are the first to present nBR reference values in CH patients and the effect of oxygen on the nBR parameters. Consequently, it is not possible to make an accurate comparison with other nBR studies.

Our results of the nBR in CH and those from the literature raise some concerns about the applicability of the BR in CH. We searched the literature for BR R2 parameters and found conflicting results with studies indicating no difference between CH patients and healthy controls,[7] a decreased excitability in CH patients based on a lower R2 amplitude,[8] or an increased excitability based on an increased R2 duration and amplitude.[9]

If we combine these variable findings with our own results of the nBR, we feel that the nBR may not be a suitable instrument for exploring the pathophysiology of CH, although a previous BR study suggested otherwise.[10] We have to emphasize that most studies measured conventional non-nociceptive BRs, nevertheless without consistent results. We studied a fairly small homogeneous group of ten male CH patients. It is desirable to study a larger population with both male and female patients comparing CH patients in the active *versus* the remission phase. Also, the addition of healthy controls is necessary to compare values between groups in further studies.

We conclude that the nBR is not different between symptomatic and asymptomatic sides in patients during the active phase of CH, outside of CH attacks, and that there is no measurable effect of oxygen

inhalation. Considering our observations with respect to the possible prophylactic action of SNS,[5] it is questionable whether it will ever be possible to accurately measure the nBR during CH attacks.

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Chapter 8

Summary & Future perspectives

Summary

The studies compiled in this thesis focus on the acute treatment of cluster headache (CH) with oxygen and predictors for its efficacy.

Chapter 2 comprises of a historical review of oxygen therapy in headache and particularly in CH.[1]

In the early 20th century, oxygen was frequently used to treat angina pectoris, which was known to be associated with vasoconstriction.[2] Possibly because migraine, which was not yet separated from CH, was also believed to be caused by vasoconstriction,[3] oxygen was tried for headache treatment likewise. During the late 1930s, an opposite view regarding the pathophysiology of 'migrainous headaches' and the oxygen effect arose: in 'migrainous headaches' there is no vasoconstriction, but vasodilatation, and oxygen probably does not control hypoxia, but probably causes vasoconstriction. The latter was already concluded in 1930.[4]

The first description of oxygen treatment in headache in 1940 did not specifically deal with CH.[5] The first recommendation of oxygen treatment for CH was in 1952, when Horton described the pain and associated symptoms of CH.[6] The reason why Horton started using oxygen as a headache treatment is not clear from his early papers. As late as in 1961 was oxygen described by Horton as a vasoconstricting agent.[7]

The efficacy of (normobaric) oxygen at flow rates of 6, 7 and 12 litre/minute (L/min) as acute CH treatment was confirmed in three clinical trials,[8, 9, 10] the first of which was published 29 years after the first recommendation.[9] From that time, oxygen was established as acute CH treatment.

Next to *normobaric* oxygen treatment, the abortive and prophylactic effects of *hyperbaric* oxygen (HBO) treatment in CH have also been explored in several studies, but no firm evidence of its efficacy was found.[11]

With (normobaric) oxygen an effective, acute CH treatment was found, the exact mechanism of which is still unclear. Only recently, it was suggested that treatment with 100% oxygen in rats acted on the parasympathetic pathways to exert its abortive effects on evoked trigeminovascular activation and autonomic pathway activation during CH attacks, rather than directly on trigeminal afferents to the dural vasculature (*i.e.* a direct vasoconstriction).[12]

In **Chapter 3** I describe a *retrospective* cross-sectional correlation study on the predictive factors for efficacy of oxygen in CH.[13]

Hundred-fifteen adult CH patients,[14] who had used oxygen for the first time less than 10 years before and at least four times, were included and assessed by means of a questionnaire (see Appendix A).

Using the Bonferroni correction for multiple testing, there were no statistically significant differences in the initial univariate analysis of diverse factors comparing the clear (oxygen) responders with the clear non-responders plus the moderate responders.[13]

A multivariate analysis on the significant variables of the initial univariate analysis, when the Bonferroni correction was not applied, showed that 'smoking in the past', a 'maximal duration of the CH attack of 180 minutes (min) or less' and 'no interictal headache' were independent factors determining oxygen response. The presence of every one of these three variables gave patients an approximately three to four times higher odds of being a responder than being a non-responder.[13]

In **Chapter 4** I describe a *prospective* cross-sectional correlation multi-centre study on the predictive factors for efficacy of oxygen in CH.[15]

The study used two questionnaires (see Appendix B and C). Ninety-four adult CH patients,[14] who took oxygen therapy for the first time and who subsequently used it in at least three CH attacks, were included. To enable a comparison with the retrospective study,[13] response to oxygen was classified in a nearly similar way.[15]

Using the Bonferroni correction for multiple testing, only a statistically significant difference in triptan use was found. Clear non-responders compared to clear responders more often used triptans in the cluster period in which they had used oxygen for the first time ever as well.[15]

Concerning a significant difference in photo- and phonophobia, found in the univariate sub-analysis when the Bonferroni correction was not applied, I place our results in the perspective of the finding that the photophobia circuits contain locations at which oxygen is presently known to exert its action in CH: the superior salivatory nucleus and vasculature.[15]

In **Chapter 5** I describe the 'rebound effect of oxygen',[16] which was defined for study purposes as 'a for the individual patient more rapid than usual recurrent CH attack after complete relief following oxygen therapy, or an increase in the number of attacks per 24 hours (h) while using oxygen therapy as acute attack treatment'.[16]

Eight patients fulfilling our definition (four from the retrospective study,[13] three from the then still ongoing prospective study [15] and one CH patient not included in either of the two studies) were reported. The report of the defined rebound effect by only 4.4% of the combined study group [16] is much less than found in literature lacking a clear definition of the rebound phenomenon.[9]

In the eight studied patients, rebound CH was not experienced after all their attacks, but on average in 87.5% of oxygen treated CH attacks. The mean duration until the next CH attack was 39 min when using oxygen *versus* 933 min without. The mean frequency was 4.1 CH attacks/day when using oxygen *versus* 2.5 CH attacks/day without.[16]

Similar to the factors predicting oxygen response, the rebound effect deserves clinical attention in daily practice.[16]

In **Chapter 6** I describe our study of the *diagnostic* nociception specific blink reflex to investigate the (direct or indirect) effect of oxygen on medullary interneurons in CH patients.[17]

The superficial nociceptive A-delta fibres of both supraorbital nerves were selectively stimulated,[18] up to a median of six series.[17]

We encountered unexpected *therapeutic and prophylactic* effects of the stimulation. These serendipitous results manifested during the study of the first seven CH patients, who were all in their cluster period or had chronic cluster headache (CCH). None of these seven patients experienced a spontaneous CH attack during the clinical study time of median 8.4 h. Furthermore, three patients, who had active CH for at least 6 months, experienced a CH attack freedom of at least 13 days following study participation.[17]

In **Chapter 7** I describe, as reference values for future studies, the collected nociception specific blink reflex R2 parameters of the study of ten male CH patients outside a CH attack, but in a cluster period or having CCH, and the effect of high-flow oxygen inhalation on these parameters.[19]

There were no significant differences in the nociception specific blink reflex R2 parameters before *versus* during and before *versus* 6 h following oxygen inhalation (n = 10 and 9 respectively), and before oxygen inhalation when the symptomatic side was compared to the asymptomatic side (n = 10).[19]

Future perspectives

The various studies of this thesis, added to those in the literature, suggested several targets for (further) studies. In addition to the discussion of the previous studies, I will briefly discuss current studies and literature on some of these different targets as a basis for further research.

Oxygen flow rates, techniques of oxygen application, breathing patterns and gas temperatures and pressures

The beneficial effect of oxygen compared to sublingual ergotamine tartrate and placebo has been shown at flow rates of 7 and 12 L/min, respectively.[9, 10] The difference in effect between 7 L/min and 12 L/min, however, has never been investigated in a controlled study. Our current ongoing CLuster headache ATtacks OXYgen Treatment (CLATOXYT) trial (trial ID NTR3801) has the primary objective to study whether there is a difference in treatment effect between these two oxygen flow rates in the acute treatment of CH attacks. This study in newly diagnosed or oxygen naïve adult CH

patients, uses a double-blind crossover design, two questionnaires and a diary. At present, approximately 90% of the targeted total number of patients has been included.

We recently reviewed the efficacy of the standard non-rebreathing masks with normobaric room temperature oxygen in relieving pain in CH.[20]

Regarding the fraction of inspired oxygen, interfaces like tusk mask variants are at least similar to the standard non-rebreathing masks, and demand valve oxygen is even superior.[20] Currently, only demand valve oxygen (in combination with initial hyperventilation) has been investigated in a pilot study as a new oxygen delivery system for the acute treatment of CH. The number of four participants was too small to draw any firm conclusions,[21] although the positive trend suggests requirement of further study in larger patient groups.

Although hyperventilation may result in an increase in partial pressure of oxygen, hypocapnia and vasoconstriction,[20] the effect of hyperventilation on pain reduction during a CH attack has not been extensively studied. Whether hyperventilation is superior to normal breathing with regard to CH pain reduction is unknown and might require further study.

In a study investigating an expected superior role of inhaled gas temperature over oxygen concentration, it was shown that inhalation of room air of 5 °C at a flow rate of 6 L/min for at least 15 min provided significant relief in 85% of eighty treated CH attacks, a result similar to 100% oxygen (with no details provided on its prescription).[22] In a pilot study, intranasal cooling to approximately 2 °C by evaporation of by perfluorohexane cooled oxygen at a ‘low’ flow rate for a maximum of 20 min provided a complete or partial pain and symptom relief immediately following treatment in 40% and 50% of twenty treated migraine attacks, respectively.[23] In conclusion, cryotherapy applied as cooled gas (room air or 100% oxygen) could have a yet underestimated therapeutic effect in neurovascular headaches. Especially, room air and not per se 100% oxygen could possibly be an effective acute treatment in CH, if cooled.[22] This could be a target for further studies.

The effects of 100% oxygen at pressures above one atmosphere (hyperbaric oxygen) have been studied in CH. The current evidence is insufficient to confirm its acute[11] or prophylactic effects.[24] A hyperbaric pressurized air mixture can be delivered by continuous positive airway pressure among others. A prophylactic effect of continuous positive airway pressure was described in a number of CH cases associated with (predominantly obstructive) sleep apnoea syndrome.[25, 26, 27, 28, 29, 30, 31] Therefore, the effect of air, not only cooled as mentioned before, but also higher pressurized, could be a target for future studies.

Calcitonin gene-related peptide, the nicotinic acetylcholine receptor and the photophobia circuits

The endogenous neuropeptide calcitonin gene-related peptide (CGRP) binds in a competitive antagonistic way with exogenous nicotine to the nicotinic acetylcholine receptor and blocks its

activation by presynaptically released acetylcholine. It is assumed to improve the signal-to-noise ratio in the synapse.[32]

CGRP has been linked to photophobia and thought to modulate nociception by enhancing transmission. CGRP receptors are found in the ventroposteromedial thalamus. The posterior thalamus is one of the levels of interaction between trigeminal pain modulating systems and photophobia.[33] The (degree of inhibitory) action of CGRP on the nicotinic acetylcholine receptor at the synapses in photophobia circuits could be a focus for further research.

In addition to the neuromodulatory actions, CGRP has neurovascular actions. It can induce facial and meningeal vasodilation, following stimulation of the trigeminal nucleus caudalis. Following this trigeminal nucleus caudalis stimulation, trigeminal CGRP release is assumed to be indirectly decreased by blockage of the nicotinic acetylcholine receptor.[34] As dural vessels do not contain functional cholinergic nicotinic acetylcholine receptors, the regulation of nicotinic acetylcholine receptors present in the sphenopalatine ganglion of the facial nerve,[35] and its interaction with CGRP at its local synapses could be a further focus for research, apart from a potential upregulation of the nicotinic acetylcholine receptors in smokers in the brain stem.[15]

Bilateral, time contingent, nociception specific, transcutaneous supraorbital nerve stimulation

Focussing on supraorbital nerve stimulation, there are anecdotal case reports that describe the efficacy in CCH of *invasive* supraorbital nerve stimulation, alone and in combinations with supratrochlear and/or infraorbital and/or occipital nerve stimulation.[36, 37, 38]

The supraorbital nerve can easily be stimulated in a *non-invasive* way, transcutaneously, which offers advantages over invasive stimulation, as described in Chapter 6.[17] It is obvious that further studies are necessary, not only on the mechanism of action of peripheral neurostimulation, but also on the potential prophylactic effect of bilateral, time contingent, nociceptive specific, transcutaneous supraorbital nerve stimulation in episodic cluster headache (ECH) and CCH.

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Chapter 9

Samenvatting & Toekomstperspectieven

Samenvatting

De studies, die in dit proefschrift zijn gebundeld, zijn gericht op de acute behandeling van clusterhoofdpijn (CH) met zuurstof en op de voorspellers van de werkzaamheid hiervan.

Hoofdstuk 2 omvat een historisch overzicht van zuurstoftherapie bij hoofdpijn en in het bijzonder bij CH.[1]

In het begin van de 20e eeuw, werd zuurstof vaak gebruikt voor de behandeling van angina pectoris, waarvan de associatie met vaatvernauwing bekend was.[2] Aangezien migraine, dat nog niet gescheiden was van CH, wellicht ook verondersteld werd te worden veroorzaakt door vasoconstrictie,[3] werd zuurstof eveneens uitgeprobeerd als hoofdpijn behandeling. In de late jaren dertig ontstond een tegenovergesteld standpunt ten aanzien van de pathofysiologie van 'migraineuze hoofdpijn' en het effect van zuurstof: bij 'migraineuze hoofdpijn' is er geen vasoconstrictie, maar vasodilatatie, en zuurstof controleert waarschijnlijk geen hypoxie, maar veroorzaakt waarschijnlijk vasoconstrictie. Dit laatste werd reeds geconcludeerd in 1930.[4]

De eerste beschrijving van zuurstoftherapie bij hoofdpijn in 1940 handelde niet specifiek over CH.[5] De eerste aanbeveling voor zuurstoftherapie voor CH was in 1952, toen Horton de pijn en de bijbehorende symptomen van CH beschreef.[6] De reden waarom Horton begon met zuurstof als hoofdpijnbehandeling wordt niet duidelijk uit zijn vroege publicaties. Pas in 1961 werd zuurstof door Horton beschreven als vasoconstrictief.[7]

De werkzaamheid van (normobare) zuurstof met stroomsnelheden van 6, 7 en 12 liter/minuut (L/min.) als acute CH behandeling werd bevestigd in drie "clinical trials",[8, 9, 10] waarvan de eerste 29 jaar na de eerste aanbeveling werd gepubliceerd.[9] Vanaf dat moment, was zuurstof gevestigd als acute CH behandeling.

Naast *normobare* zuurstoftherapie, werden ook de abortieve en profylactische effecten van *hyperbare* zuurstoftherapie (HBO) bij CH onderzocht in een aantal studies, echter er werd geen hard bewijs voor de werkzaamheid hiervan gevonden.[11]

Met (normobare) zuurstof was een effectieve, acute CH behandeling gevonden, waarvan het exacte mechanisme nog steeds onduidelijk is. Pas recent werd gesuggereerd dat behandeling met 100% zuurstof bij ratten werkt op parasympatische "pathways", om daar zijn abortieve effecten op opgewekte trigeminovasculaire activatie en autonome "pathway" activatie tijdens CH aanvallen uit te oefenen, in plaats van rechtstreeks op trigeminale afferenten naar durale vaten (dat wil zeggen een directe vaatvernauwing).[12]

In **Hoofdstuk 3** beschrijf ik een *retrospectieve* cross-sectionele correlatiestudie naar de voorspellende factoren voor de werkzaamheid van zuurstof bij CH.[13]

Honderdvijftien volwassen CH patiënten,[14] die zuurstof voor het eerst minder dan 10 jaar ervoor en tenminste vier keer hadden gebruikt, werden geïncludeerd en in kaart gebracht met behulp van een vragenlijst (zie Bijlage A).

Gebruik makend van de Bonferroni-correctie voor “multiple testing”, waren er geen statistisch significante verschillen in de initiële univariate analyse van diverse factoren, die de “clear (oxygen) responders” met de “clear non-responders” én de “moderate responders” vergeleek.[13]

Een multivariate analyse van de significante variabelen van de initiële univariate analyse, wanneer de Bonferroni-correctie niet werd toegepast, liet zien dat 'roken in het verleden', een 'maximale duur van de CH aanval van 180 minuten (min.) of minder' en 'geen interictale hoofdpijn' onafhankelijk factoren waren, die de respons op zuurstof bepaalden. De aanwezigheid van elk van deze drie variabelen gaf patiënten een ongeveer drie tot vier maal hogere kans een “responder” dan een “non-responder” te zijn.[13]

In **Hoofdstuk 4** beschrijf ik een *prospectieve* cross-sectionele correlatie multicenter studie naar de voorspellende factoren voor de werkzaamheid van zuurstof bij CH.[15]

De studie maakte gebruik van twee vragenlijsten (zie Bijlage B en C). Vierennegentig volwassen CH patiënten,[14] die voor het eerst zuurstoftherapie kregen en dit vervolgens gebruikten bij tenminste drie CH aanvallen, werden geïncludeerd. Om een vergelijking met de retrospectieve studie mogelijk te maken,[13] werd de respons op zuurstof op nagenoeg dezelfde wijze geclassificeerd.[15]

Gebruik makend van de Bonferroni-correctie voor “multiple testing”, werd alleen een statistisch significant verschil in triptaan gebruik gevonden. In vergelijking met “clear responders” gebruikten “clear non-responders” veel vaker triptanen in de clusterperiode, waarin ze eveneens zuurstof voor de eerste keer ooit gebruikten.[15]

Betreffende een significant verschil in foto- en fonofobie, gevonden in de univariate sub-analyse wanneer de Bonferroni-correctie niet werd toegepast, plaats ik onze resultaten in het perspectief van de vaststelling dat de fotofobie circuits lokalisaties bevatten, waarvan thans bekend is dat zuurstof er zijn werking uitoefent bij CH: de “superior salivatory nucleus” en de vasculatuur.[15]

In **Hoofdstuk 5** beschrijf ik het ‘rebound effect van zuurstof ',[16] dat voor studiedoeleinden gedefinieerd was als ‘een voor de individuele patiënt sneller dan normaal recidiverende CH aanval na volledige verlichting door zuurstoftherapie, of een toename van het aantal aanvallen per 24 uur (u.), terwijl zuurstoftherapie als acute aanvalsbehandeling gebruikt wordt'.[16]

Acht patiënten, die aan onze definitie beantwoordden (vier uit de retrospectieve studie, [13] drie uit de toen nog lopende prospectieve studie[15] en een CH patiënt, die niet in een van de twee studies geïncludeerd was), werden beschreven. De rapportage van het gedefinieerde “rebound effect” door slechts 4,4% van de gecombineerde studiegroep[16] is veel minder dan gevonden in de literatuur, waar een duidelijke definitie van het “rebound” fenomeen ontbrak.[9]

De acht onderzochte patiënten ervoeren “rebound” CH niet na al hun aanvallen, maar bij gemiddeld 87,5% van de met zuurstof behandelde CH aanvallen. De gemiddelde duur tot de volgende CH aanval was 39 min. bij het gebruik van zuurstof *versus* 933 min. zonder. De gemiddelde frequentie was 4,1 CH aanvallen/dag bij het gebruik van zuurstof *versus* 2,5 CH aanvallen/dag zonder.[16]

Net als bij de factoren die de zuurstofrespons voorspellen, verdient het “rebound effect” klinische aandacht in de dagelijkse praktijk.[16]

In **Hoofdstuk 6** beschrijf ik onze studie van de *diagnostische* nociceptief specifieke blink reflex, om het (directe of indirecte) effect van zuurstof op medullaire interneuronen bij CH patiënten te onderzoeken.[17]

De superficiële, nociceptieve A-delta vezels van beide *nn supraorbitales* werden selectief gestimuleerd,[18] tot een gemiddelde van zes series.[17]

We kwamen onverwachte *therapeutische en profylactische* effecten van de stimulatie tegen. Deze serendiepe resultaten manifesteerden zich tijdens de studie van de eerste zeven CH patiënten, die allemaal in hun clusterperiode waren of chronische clusterhoofdpijn (CCH) hadden. Geen van deze zeven patiënten ervoer een spontane CH aanval tijdens de klinische studietijd met een mediaan van 8,4 u. Bovendien ervoeren drie patiënten, die actieve CH hadden sinds tenminste 6 maanden, een CH aanvalsvrijheid van tenminste 13 dagen na studieparticipatie.[17]

In **Hoofdstuk 7** beschrijf ik, als referentiewaarden voor toekomstige studies, de verzamelde nociceptief specifieke blink reflex R2 parameters van de studie van tien mannelijke CH patiënten buiten een CH aanval, maar in een clusterperiode of met CCH, en het effect van inhalatie van zuurstof met een hoge stroomsnelheid op deze parameters.[19]

Er waren geen significante verschillen in de nociceptief specifieke blink reflex R2 parameters voor *versus* tijdens en voor *versus* 6 u. na zuurstofinhalatie (n = 10 en 9 respectievelijk), en voor zuurstofinhalatie wanneer de symptomatische zijde vergeleken werd met de asymptomatische zijde (n = 10).[19]

Toekomstperspectieven

De verschillende studies van dit proefschrift, toegevoegd aan die in de literatuur, suggereren verschillende doelen voor (verdere) studies. In aanvulling op de bespreking van de voorgaande studies, zal ik kort ingaan op de huidige studies en literatuur van een aantal van deze verschillende doelen, als basis voor verder onderzoek.

Zuurstofstroomsnelheden, technieken van zuurstoftoediening, ademhalingspatronen en gastemperaturen en -drukken

Het gunstigere effect van zuurstof ten opzichte van sublinguaal ergotamine tartraat en placebo is aangetoond bij stroomsnelheden van 7 en 12 L/min., respectievelijk.[9, 10] Het verschil in werkzaamheid tussen 7 L/min. en 12 L/min. is echter nooit onderzocht in een gecontroleerde studie. Onze huidige, lopende "CLuster headache ATtacks OXYgen Treatment (CLATOXYT) trial" (trial ID NTR3801) heeft het primaire doel om te onderzoeken of er een verschil in behandelingseffect bestaat tussen deze twee zuurstofstroomsnelheden bij de acute behandeling van CH aanvallen. Deze studie bij nieuw gediagnosticeerde of zuurstof naïeve volwassen CH patiënten, maakt gebruik van een dubbelblind "crossover design", twee vragenlijsten en een dagboek. Op dit moment is ongeveer 90% van het beoogde, totale aantal patiënten geïncludeerd.

We hebben onlangs de werkzaamheid van de standaard "non-rebreathing" maskers, met normobare zuurstof op kamertemperatuur, bij het verlichten van pijn bij CH, herbekeken.[20]

Betreffende de fractie van ingeademde zuurstof, zijn "interfaces" zoals "tusk masker" varianten tenminste gelijk aan de standaard "non-rebreathing" maskers, en is "demand valve oxygen" zelfs superieur.[20] Momenteel is alleen "demand valve oxygen" (in combinatie met een initiële hyperventilatie) onderzocht in een pilot studie als nieuw zuurstoftoedieningssysteem bij de acute behandeling van CH. Het aantal van vier deelnemers was te klein om harde conclusies te trekken, hoewel de positieve trend de noodzaak tot verder onderzoek in grotere patiëntengroepen suggereert.[21]

Hoewel hyperventilatie kan resulteren in een toename van de partiële zuurstofdruk, hypocapnie en vasoconstrictie,[20] is het effect van hyperventilatie op pijnverlichting tijdens een CH aanval niet uitgebreid onderzocht. Of hyperventilatie superieur is aan een normale ademhaling met betrekking tot pijnvermindering bij CH is onbekend en zou verder onderzoek kunnen vereisen.

In een studie, waarin een verwachte superieure rol van de temperatuur van geïnhaleerd gas boven de zuurstofconcentratie werd onderzocht, werd aangetoond dat de inhalatie van kamerlucht van 5 °C met een stroomsnelheid van 6 L/min. gedurende tenminste 15 min. een significante verlichting gaf bij 85% van de tachtig behandelde CH aanvallen, een resultaat vergelijkbaar met 100% zuurstof (waarvan geen details werden verstrekt over de toediening).[22] In een pilot studie gaf intranasale afkoeling tot ongeveer 2 °C, door verdamping van door perfluorhexaan gekoeld zuurstof, bij een 'lage' stroomsnelheid gedurende een maximum van 20 min. een volledige of partiële pijn- en symptoomverlichting onmiddellijk na de behandeling bij 40% en 50% van twintig behandelde migraine aanvallen, respectievelijk.[23] Concluderend kan cryotherapie, toegediend als gekoeld gas (kamerlucht of 100% zuurstof), een nog onderschat therapeutisch effect bij neurovasculaire hoofdpijn hebben. Vooral kamerlucht, en niet per sé 100% zuurstof, kan mogelijk een effectieve acute behandeling bij CH zijn, als gekoeld.[22] Dit zou een doel kunnen zijn voor verdere studies.

De effecten van 100% zuurstof met een druk boven één atmosfeer (hyperbare zuurstof) zijn bestudeerd bij CH. Het huidige bewijs is onvoldoende om acute[11] of profylactische effecten ervan te bevestigen.[24] Een hyperbaar perslucht mengsel kan onder andere geleverd worden door “continuous positive airway pressure”. Een profylactisch effect van “continuous positive airway pressure” werd beschreven in een aantal CH casussen geassocieerd met (voornamelijk obstructief) slaapapneu syndroom.[25, 26, 27, 28, 29, 30, 31] Derhalve zou het effect van lucht, niet alleen gekoeld zoals eerder vermeld, maar ook met hogere drukken een doel kunnen zijn voor toekomstige studies.

“Calcitonin gene-related peptide”, de nicotinerge acetylcholine receptor en de fotofobie circuits

Het endogene neuropeptide “calcitonin gene-related peptide” (CGRP) bindt op een competitieve, antagonistische wijze met exogeen nicotine aan de nicotinerge acetylcholinereceptor en blokkeert de activering ervan door presynaptisch vrijgemaakt acetylcholine. Het wordt verondersteld de signaal-ruisverhouding in de synaps te verbeteren.[32]

CGRP is gelinkt aan fotofobie en wordt verondersteld nociceptie te moduleren door de transmissie te vergroten. CGRP-receptoren worden gevonden in de ventroposteriomediale thalamus. De posterieure thalamus is een van de niveaus van interactie tussen trigeminale pijn modulerende systemen en fotofobie.[33] De (mate van inhibitoire) werking van CGRP op de nicotinerge acetylcholinereceptor in de synapsen in fotofobie circuits zou een focus voor verder onderzoek kunnen zijn.

Naast de neuromodulatoire werkingen heeft CGRP ook neurovasculaire werkingen. Het kan faciale en meningeale vasodilatatie induceren na stimulatie van de trigeminale nucleus caudalis. Volgend op deze trigeminale nucleus caudalis stimulatie, wordt verondersteld dat trigeminale CGRP-vrijmaking indirect wordt verminderd door blokkering van de nicotinerge acetylcholinereceptor.[34] Omdat durale vaten geen functionele, cholinerge, nicotinerge acetylcholinereceptoren bevatten, zou de regulatie van nicotinerge acetylcholinereceptoren aanwezig in het ganglion sfenopalatinum van de n facialis,[35] en de interactie ervan met CGRP ter hoogte van de lokale synapsen, een focus kunnen zijn voor verder onderzoek, nog afgezien van een mogelijke opregulatie van de nicotinerge acetylcholinereceptoren bij rokers in de hersenstam.[15]

Bilaterale, tijdcontingente, nociceptief specifieke, transcutane supraorbitale zenuwstimulatie

Gericht op supraorbitale zenuwstimulatie zijn er anekdotische “case reports”, die bij CCH de werkzaamheid beschrijven van *invasieve* supraorbitale zenuwstimulatie, alleen en in combinatie met supratrochleaire en/of infraorbitale en/of occipitale zenuwstimulatie.[36, 37, 38]

De *n supraorbitalis* kan gemakkelijk worden gestimuleerd op een *niet-invasieve* wijze, transcutaan, wat voordelen biedt ten opzichte van invasieve stimulatie, zoals beschreven in hoofdstuk 6.[17] Het is duidelijk dat verdere studies nodig zijn, niet alleen naar het werkingsmechanisme van perifere neurostimulatie, maar ook naar het mogelijke, profylactische effect van bilaterale, tijdcontingente, nociceptief specifieke, transcutane supraorbitale zenuwstimulatie bij episodische clusterhoofdpijn (ECH) en CCH.

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Dankwoord

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Curriculum vitae

Curriculum vitae

Danielle Yvonne Peter Haane werd geboren op 25 juni 1981 te Boxtel.

Na het behalen van het VWO diploma in 1999 aan het Stella Maris College te Meerssen, studeerde zij Tandheelkunde aan de Katholieke Universiteit te Nijmegen, waarbij zij haar Propedeuse behaalde in 2000. Daarna studeerde zij Geneeskunde aan de Universiteit Maastricht te Maastricht. Zij behaalde haar Propedeuse in 2001, haar Doctoraal in 2004 (Predicaat: *cum laude*) en haar Basisartsexamen in 2006 (Predicaat: *cum laude*).

Van 2006 tot 2007 werkte Danielle als AGNIO (assistent-geneeskundige niet in opleiding) bij de afdeling Neurologie in het Maaslandziekenhuis te Sittard, en in 2007 als AGNIO bij de afdeling Neurologie in het Atrium Medisch Centrum te Heerlen. Van 2008 tot 2013 was Danielle AIOS (arts in opleiding tot specialist) Neurologie in het Atrium Medisch Centrum te Heerlen. In 2013 rondde zij haar specialisatie Neurologie af.

Vanaf 2013 tot heden is Danielle werkzaam als neuroloog in het Mariaziekenhuis Noord-Limburg te Overpelt, België. Daarnaast is zij sinds 2015 tot heden een dag in de week werkzaam als neuroloog op de Stadspoli van het Maastricht UMC+ te Maastricht.

In de periode van 2010 tot heden deed zij promotieonderzoek naar clusterhoofdpijn en zuurstoftherapie met als promotor Prof. dr. M.D. Ferrari, Universiteit Leiden.

Lijst van publicaties

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Haane DY, Plaum A, Koehler PJ, *et al.* High-flow oxygen therapy in cluster headache patients has no significant effect on nociception specific blink reflex parameters: a pilot study. *J Headache Pain* 2016; 17: 7.

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Appendices

Appendix A

Vragenlijst voor onderzoek naar

clusterhoofdpijn en zuurstoftherapie

Atrium Medisch Centrum Heerlen
Leids Universitair Medisch Centrum

Naam: ……..

Geboortedatum: ……

Informatiebrief: Onderzoek naar clusterhoofdpijn en zuurstoftherapie

Heerlen, januari 2009

Geachte heer, geachte mevrouw,

Wij zijn in het Atrium Medisch Centrum Heerlen een nieuw onderzoek begonnen naar het effect van zuurstoftherapie bij clusterhoofdpijn. We zouden hiervoor uw aandacht willen vragen omdat u als clusterhoofdpijnpatiënt deel zou kunnen nemen aan dit onderzoek. Hieronder volgt een korte toelichting over het onderzoek.

Zoals u wellicht weet is clusterhoofdpijn een aanvalsgewijze, hevige, borende, eenzijdige hoofdpijn waarbij ook verschijnselen aan het oog en/of neus, en bewegingsdrang kunnen optreden. De behandeling van een aanval van clusterhoofdpijn kan naast het geven van medicijnen ook bestaan uit het toedienen van zuurstof tijdens de aanval. Niet alle patiënten worden echter evenveel geholpen met zuurstof. Het is niet bekend welke patiënten wel en welke patiënten niet reageren op zuurstof.

Dit onderzoek heeft als doel te bekijken of er verschillen zijn tussen de groep met clusterhoofdpijnpatiënten die wel op zuurstoftherapie reageert en de groep clusterhoofdpijnpatiënten die niet op zuurstoftherapie reageert. Verschillen tussen deze twee groepen zouden bijvoorbeeld kunnen zijn de leeftijd, het gewicht van de patiënten of bijvoorbeeld het optreden van bewegingsdrang. Met behulp van deze gegevens proberen we de oorzaak van het ontstaan van clusterhoofdpijn beter te begrijpen en zouden we in de toekomst kunnen bepalen bij wie er wel en bij wie er geen zuurstoftherapie geprobeerd wordt.

Wij hopen daarom dat u mee zou willen werken aan dit onderzoek. Dit houdt voor u enkel in dat u de bijgevoegde vragenlijst invult en retourneert met de bijgevoegde enveloppe. Hiervoor is geen postzegel nodig. Omdat wij de gegevens van dit onderzoek zo snel mogelijk in de praktijk willen toepassen zouden wij het op prijs stellen als u de vragenlijst voor 1 april 2009 zou kunnen retourneren.

Voor vragen kunt u contact opnemen met de research assistente Tiny Simons-Sporken (tel: 045-5766713 of sein 46-6704), of u kunt zich door laten verbinden via het algemene telefoonnummer van het ziekenhuis (045 -576 66 66) met de onderzoekers; semi-arts A. Backx (sein 46-7673) of neuroloog in opleiding D. Haane (sein 46-6718).

De vragenlijst wordt vertrouwelijk behandeld en anoniem verwerkt.

We willen u bedanken voor uw tijd en voor uw bijdrage aan het onderzoek.

Met vriendelijke groet,

Dr. P. Koehler, neuroloog
Drs. D. Haane, neuroloog in opleiding
A. Backx, semi-arts neurologie

Afdeling neurologie Atrium Medisch Centrum Heerlen.

Toestemmingsverklaring:

Wij willen u vragen het onderstaande naar waarheid in te vullen zodat u toestemming geeft voor het gebruiken van uw gegevens tijdens dit onderzoek.

Ik, ……... heb de bijgevoegde informatiebrief over het onderzoek naar clusterhoofdpijn en zuurstoftherapie gelezen en begrepen. Door het zetten van mijn handtekening **ga ik akkoord** met de verwerking van de door mij ingevulde vragenlijst ten behoeve van het genoemde onderzoek.

Datum…… Handtekening deelnemer:……

Datum…… Handtekening onderzoeker:……

Vragenlijst clusterhoofdpijn en zuurstoftherapie:

Deze vragenlijst bestaat uit vier soorten vragen. Bij de meerkeuze vragen kunt u één rondje (0) aankruisen met het juiste antwoord, soms kunt u op de stippellijn uw antwoord nog aanvullen. Bij de vragen waar 'Ja/Nee' achter staat kunt u omcirkelen wat voor u van toepassing is. Ook bij de vragen waar 'helemaal/veel/weinig/niets' staat kunt u invullen wat voor u van toepassing is. Bij de open vragen moet u in uw eigen woorden een korte omschrijving geven.

I: Algemene gegevens:

1. Wat was uw leeftijd bij ontstaan van de klachten van clusterhoofdpijn?. . . . . .

2. Wat was uw leeftijd bij het stellen van de diagnose clusterhoofdpijn?. . . . . .

3. Door wie is de diagnose clusterhoofdpijn gesteld? Huisarts/Neuroloog.

4. Wat is uw lengte en gewicht nu?
   Lengte:…….. Gewicht: …….

5. En wat waren uw lengte en gewicht bij ontstaan van de hoofdpijn?
   Lengte:……... Gewicht: ……

6. Wat is uw beroep? ……..

7. Rookt u, of heeft u gerookt in het verleden?
Ja/Nee (Indien nee ga verder naar vraag 11)

8. Hoeveel sigaretten per dag rookt u nu per dag? …….

9. Hoelang rookt u al? ……

10. Hoeveel sigaretten heeft u in het verleden per dag gerookt en voor hoelang?
    . . . . . sigaretten per dag, gedurende . . . . . jaar
    . . . . . sigaretten per dag, gedurende . . . . . jaar
    . . . . . sigaretten per dag, gedurende . . . . . jaar

11. Gebruikt u alcohol, of heeft u in het verleden alcohol gebruikt?
Ja/Nee (Indien nee ga verder naar vraag 13)

12. Hoe vaak per week drinkt u alcohol bevattende dranken? ……..

13. Op een typische dag dat u alcohol gebruikt, hoeveel drankjes zijn dat dan?…….

14. Hoeveel glazen alcohol heeft u in het verleden per week gebruikt? …….

15. Heeft u in het verleden te maken gehad met onderstaande ziekten/aandoeningen?
    a. Slaapapneu syndroom? Ja/Nee
    b. Andere vormen van hoofdpijn? Ja/Nee
    c. Hersenschudding? Ja/Nee

16. Gebruikt u medicijnen voor andere ziekten/aandoeningen dan clusterhoofdpijn?

……..	……..
……..	……..
……..	……..

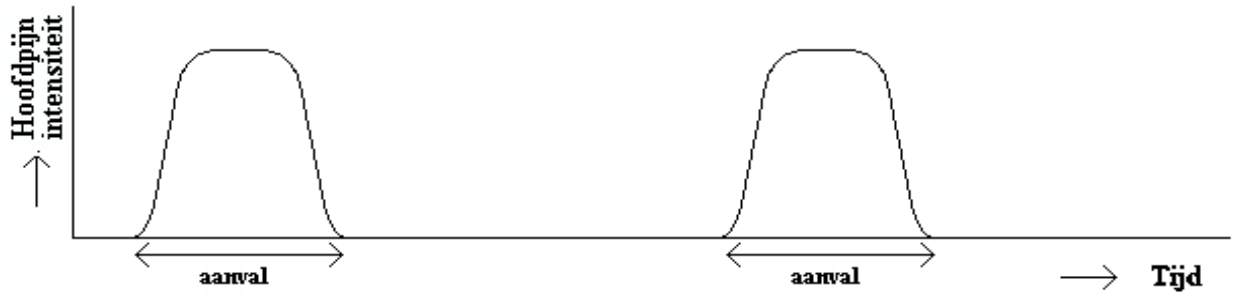
17. Komt er bij u in de familie clusterhoofdpijn voor? ……

II: Clusterhoofdpijn specifieke gegevens:

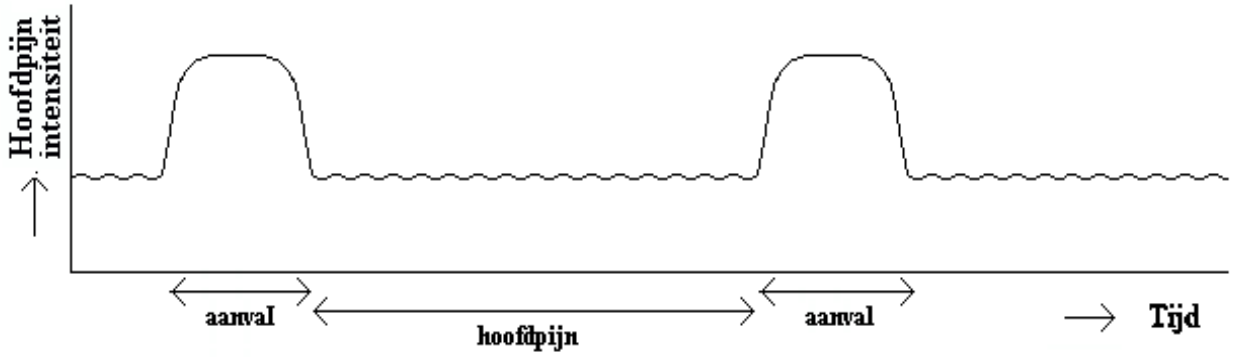
Hieronder volgt eerst algemene informatie over clusterhoofdpijn en wat er precies bedoeld wordt met een clusterhoofdpijn*aanval*, een cluster*periode* en de piekfase.

De clusterhoofdpijnaanval:
Deze vragenlijst gaat over het voorkomen van clusterhoofdpijn. Deze hoofdpijn kan voorkomen in aanvallen. Een aanval wil zeggen dat de hoofdpijn vrij plotseling begint, toeneemt tot een hoogtepunt, enkele minuten/uren of dagen achtereen aanhoudt, en vervolgens weer duidelijk afneemt. De aanvallen zijn dus vrij scherp begrensd. Tussen de aanvallen in is er geen hoofdpijn (zie plaatje 1), of is de hoofdpijn duidelijk verminderd (zie plaatje 2).

Plaatje 1

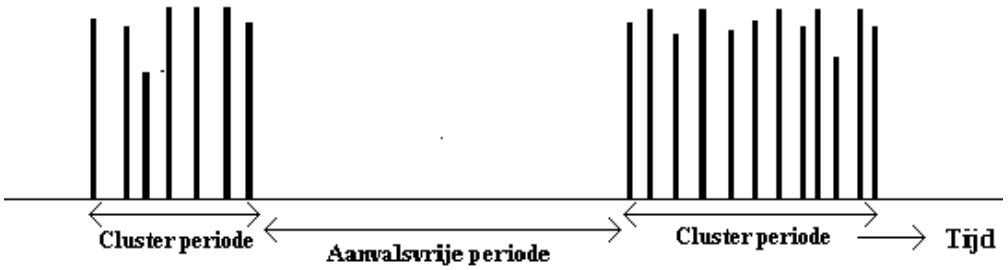


Plaatje 2



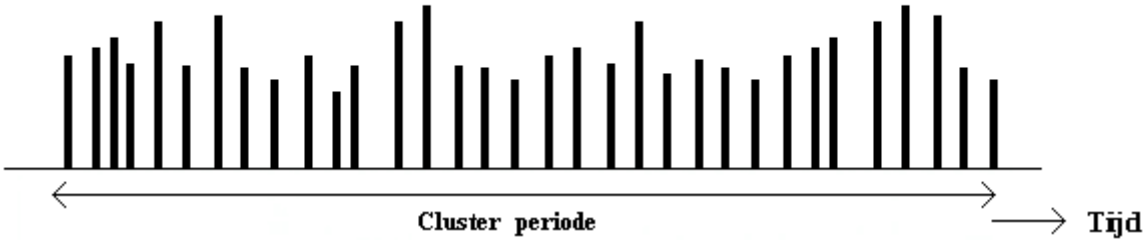
De clusterperiode:
Aanvallen van hoofdpijn kunnen in clusterperiodes voorkomen. Een clusterperiode is een periode van enige weken tot enkele maanden, waarin de aanvallen van hoofdpijn zeer frequent voorkomen (soms meerdere malen per dag). Tussen de clusterperiodes zit een aanvalsvrije periode van weken, maanden of zelfs jaren (zie plaatje 3: 1 verticale streep is een clusterhoofdpijnaanval, de groepen aanvallen is een clusterperiode). Als dit het geval is, spreekt men van episodische clusterhoofdpijn.

Plaatje 3



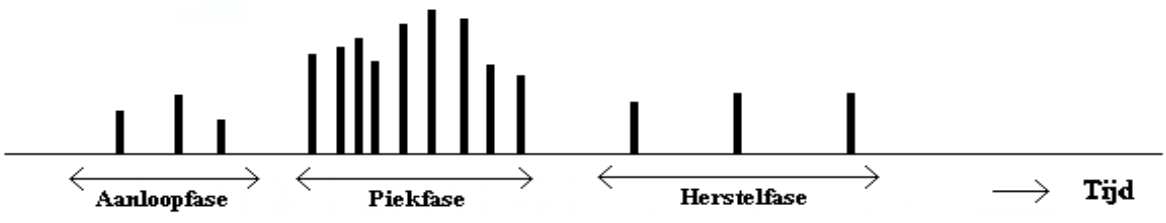
Echter, in een klein percentage van de gevallen is er sprake van chronische clusterhoofdpijn. Hierbij treden de aanvallen vrijwel dagelijks of wekelijks op, zonder duidelijke, lange aanvalsvrije perioden (zie plaatje 4).

Plaatje 4



De piekfase van een clusterperiode:
De frequentie van aanvallen tijdens een clusterperiode kan verschillen (zie plaatje 5). In de aanloopfase zijn er meestal relatief weinig aanvallen. Vaak wordt de aanloopfase gevolgd door een periode met zeer frequente aanvallen (de piekfase). Deze aanvallen duren vaak langer dan de aanvallen in de aanloopfase. Aan het eind van een clusterperiode nemen de frequentie en de duur van de aanvallen meestal weer af (herstelfase).

Plaatje 5



18. Hoe zou u de hoofdpijn tijdens een aanval omschrijven?
- o borend of kloppend
- o stekend, alsof er messen in het hoofd worden gestoken
- o het gevoel alsof het oog eruit gedrukt wordt
- o anders, nl……..

19. Bent u pijnvrij in de periode tussen de aanvallen (plaatje 1) of heeft u tussen de hoofdpijnaanvallen minder hoofdpijn (plaatje 2)?
- o Pijnvrij (plaatje 1)
- o Minder hoofdpijn (plaatje 2)

20. Hoe lang duurt een aanval (plaatje 1-2) gemiddeld als u ***geen*** medicijnen gebruikt? (graag 1 antwoord geven)
- o korter dan 15 minuten, namelijk……minuten
- o 15 minuten tot 3 uur, namelijk……minuten
- o langer dan 3 uur, namelijk ……uur
- o weet niet

21. Hoe lang duurt een aanval minimaal als u ***geen*** medicijnen gebruikt? (graag 1 antwoord geven)
- o korter dan 15 minuten, namelijk……minuten
- o 15 minuten tot 3 uur, namelijk ……minuten
- o langer dan 3 uur, namelijk …….uur
- o weet niet

22. Hoe lang duurt een aanval maximaal als u ***geen*** medicijnen gebruikt? (graag 1 antwoord geven)
- o korter dan 15 minuten, namelijk……minuten
- o 15 minuten tot 3 uur, namelijk ……minuten
- o langer dan 3 uur, namelijk……..uur
- o weet niet

23. Komen de aanvallen van hoofdpijn bij u in clusterperiodes met daartussen periodes van weken, maanden of jaren waarin u aanvalsvrij bent (zie plaatje 3)?
- o Ja. ***Ga verder met de vragen 24 t/m 33 op bladzijde X.***
- o Nee (dit betekent dat u geen aanvalsvrije periodes hebt, zie plaatje 4). ***Ga verder met de vragen 34 t/m 38 op bladzijde Y.***
- o Vroeger wel, maar nu niet meer (dit wil zeggen dat u nu geen aanvalsvrije perioden meer hebt, zie plaatje 4). ***Ga verder met de vragen 34 t/m 38 op bladzijde Y.***
- o Vroeger niet, maar nu wel (dit betekent dat u momenteel tussen de clusterperiodes wel aanvalsvrije periodes hebt, zie plaatje 3). ***Ga verder met de vragen 24 t/m 33 op bladzijde X.***

Vraag 24 t/m 33 zijn bedoeld voor mensen die *wel aanvalsvrije perioden* hebben.

24. Hoe vaak heeft u gemiddeld aanvallen van clusterhoofdpijn in de piekfase (zie plaatje 5)?
    - o ……. keer per dag
    - o ……. keer per week

25. Hoe vaak heeft u minimaal last van aanvallen van clusterhoofdpijn in de piekfase?
    - o ……. keer per dag
    - o ……. keer per week

26. Hoe vaak heeft u maximaal last van aanvallen van clusterhoofdpijn in de piekfase?
    - o ……. keer per dag
    - o ……. keer per week

27. Hoe lang duurt een clusterperiode (plaatje 3) gemiddeld? (graag 1 antwoord geven)
    - o ……. weken
    - o ……. maanden
    - o ……. jaren

28. Hoe lang duurt een clusterperiode minimaal? (graag 1 antwoord geven)
    - o ……. weken
    - o ……. maanden
    - o ……. jaren

29. Hoe lang duurt een clusterperiode maximaal? (graag 1 antwoord geven)
    - o ……. weken
    - o ……. maanden
    - o ……. jaren

30. Hoe lang duurt een aanvalsvrije periode (plaatje 3) gemiddeld (dus de periode tussen twee clusters in)? (graag 1 antwoord geven)
    - o ……. weken
    - o ……. maanden
    - o ……. jaren

31. Hoe lang duurt een aanvalsvrije periode minimaal? (graag 1 antwoord geven)
    - o ……. weken
    - o ……. maanden
    - o ……. jaren

32. Hoe lang duurt een aanvalsvrije periode maximaal? (graag 1 antwoord geven)
    - o ……. weken
    - o ……. maanden
    - o ……. jaren

33. Hoe vaak hebt u een clusterperiode? (graag 1 antwoord geven)
    - o ……. keer per jaar
    - o eens in de ……. jaar

Ga verder met de vragen 39 t/m 68 op bladzijde Z.

Vraag 34 t/m 36 zijn bedoeld voor mensen die *geen aanvalsvrije perioden* hebben.

34. Hoe vaak hebt u gemiddeld aanvallen? (graag 1 antwoord geven)
    - o ……. keer per dag
    - o ……. keer per week
    - o ……. keer per maand
    - o ……. keer per jaar

35. Hoe vaak hebt u minimaal aanvallen? (graag 1 antwoord geven)
    - o ……. keer per dag
    - o ……. keer per week
    - o ……. keer per maand
    - o ……. keer per jaar

36. Hoe vaak hebt u maximaal aanvallen? (graag 1 antwoord geven)
    - o ……. keer per dag
    - o ……. keer per week
    - o ……. keer per maand
    - o ……. keer per jaar

Vraag 37 en 38 zijn bedoeld voor mensen die *geen aanvalsvrije perioden meer* hebben.

37. Hoe oud was u toen er geen aanvalsvrije perioden meer optraden?
    ……. jaar

38. Hebt u zelf een idee waardoor het komt dat de aanvalsvrije perioden zijn weggebleven?

_____

_____

_____

_____

Ga verder met de vragen 39 t/m 68 op bladzijde Z.

Vraag 39 t/m 68 zijn bedoeld voor *iedereen*, dus zowel mensen met als mensen zonder aanvalsvrije periode.

39. Hoe ernstig is de pijn? (kruis 1 van de onderstaande opties aan)
    - o Matig, er wordt geen of enige hinder ondervonden van de hoofdpijn
    - o Hevig, de dagelijkse activiteiten kunnen met moeite gedaan worden
    - o Ondraaglijk, onmogelijk om met de dagelijkse activiteiten door te gaan

40. Waar zit de pijn? ……..

41. Heeft u pijn altijd aan 1 zijde van het hoofd? ……
    a. Zo ja, welke zijde? ……..

42. Heeft u pijn in/achter de ogen, bij de slapen of tanden?……

43. Als u hoofdpijn heeft, heeft u dan ook

a.	Roodheid van het oog aan de kant van de hoofdpijn?	Ja/Nee
b.	Tranen van het oog aan de kant van de hoofdpijn?	Ja/Nee
c.	Een dichtzittende neus aan de kant van de hoofdpijn?	Ja/Nee
d.	Een loopneus aan de kant van de hoofdpijn?	Ja/Nee
e.	Hangend ooglid aan de kant van de hoofdpijn?	Ja/Nee
f.	Nauwere pupil aan de kant van de hoofdpijn?	Ja/Nee
g.	Misselijkheid en/of braken?	Ja/Nee
h.	Last van fel licht en/of hard geluid?	Ja/Nee
i.	Bewegingsdrang?	Ja/Nee

44. Wat merkt u voorafgaand aan de clusterhoofdpijnaanval?
……

45. Zoekt u tijdens een aanval wel eens de koude op?
Ja/Nee (indien nee ga verder naar vraag 48)

46. Op welke manier zoekt u de koude op? ……

47. Hoeveel heeft de koude de pijn doen verbeteren?
Helemaal/veel/weinig/niets

48. Heeft u de hoofdpijn op vaste tijdstippen op de dag?……

49. Heeft u ook ’s nachts hoofdpijn?
Ja/Nee (indien nee ga verder met vraag 51)

50. Als u ’s nachts hoofdpijn heeft wat doet u dan? ……

51. Heeft u ooit zuurstof gebruikt bij een aanval van clusterhoofdpijn?
Ja/Nee (indien nee ga naar vraag 60)

52. Hoe oud was u toen u voor het eerst zuurstof gebruikte? ……

53. Hoeveel liter zuurstof per minuut gebruikte u? …….

54. Hoeveel minuten na het begin van de hoofdpijn begon u met zuurstof? ……

55. Hoeveel verlichting van de pijn kreeg u door de zuurstof?
Helemaal/veel/weinig/niets

56. Na hoeveel tijd aan de zuurstof voelde u verlichting? ……..

57. Na hoeveel tijd aan de zuurstof was de hoofdpijn over? ……

58. Hoe vaak heeft u de zuurstof gebruikt met goed effect (veel of helemaal verbeterd) ?
…….…….

59. Indien de zuurstof na verloop van tijd minder effect heeft gekregen, na hoeveel weken/ maanden/ jaren was dat dan? ……..

60. Heeft u ooit triptanen zoals imigran/sumatriptan gebruikt tegen de hoofdpijn?
Ja/Nee (indien nee ga verder met vraag 63)

61. Was dit een injectie, neusspray, zetpil of tablet van 50 mg of 100 mg? …….

62. Hoeveel heeft dit medicijn de pijn doen verbeteren?
Helemaal/veel/weinig/niets

63. Heeft u ooit verapamil (isoptin) gebruikt tegen de hoofdpijn?
Ja/Nee (indien nee ga verder met vraag 65)

64. Hoeveel heeft verapamil (isoptin) de pijn doen verbeteren?
Helemaal/veel/weinig/niets

65. Heeft u ooit andere medicijnen gebruikt tegen de hoofdpijn? Ja/Nee
   a. Zo ja, welke? ……..

   b. Hoeveel hebben deze medicijnen de pijn doen verbeteren?
      Helemaal/veel/weinig/niets

III. Beperking dagelijks functioneren:

66. Wordt u door de hoofdpijn tijdens de clusterperiode (of tijdens een periode dat u veel aanvallen heeft als u geen duidelijke clusterperiode heeft) beperkt bij dagelijkse bezigheden? Zet een kruisje in het juiste vakje.

	helemaal niet beperkt	beetje beperkt	ernstig beperkt
1. Forse inspanning zoals hardlopen, tillen van zware voorwerpen, deelnemen aan een veeleisende sport			
2. Matige inspanning zoals een tafel verplaatsen, stofzuigen, zwemmen of fietsen			
3. Boodschappen tillen/dragen			
4. Een trap oplopen			
5. Bukken, knielen of hurken			
6. Meer dan een kilometer lopen			
7. Uzelf wassen of aankleden			

67. In hoeverre hebben uw lichamelijke gezondheid of emotionele problemen tijdens de clusterperiode (of tijdens een periode waarin u aanvallen heeft) u gehinderd in uw normale omgang met familie, vrienden, buren of bij activiteiten in groepsverband?

Helemaal niet/ enigszins/ nogal/ vrij veel/ ernstig

68. In welke mate bent u tijdens de clusterperiode (of tijdens een periode waarin u aanvallen heeft) door pijn gehinderd in uw normale werk (zowel werk buitenshuis als huishoudelijk werk)?

Helemaal niet/ klein beetje/ nogal/ vrij veel/ ernstig

- Hartelijk dank voor het invullen van de vragenlijst –
NB. Bent u niet vergeten de toestemmingsverklaring op bladzijde A in te vullen?

Appendix B

Vragenlijst 1: Zuurstoftherapie bij Clusterhoofdpijn
Atrium Medisch Centrum Heerlen, Afdeling Neurologie

Graag invullen zoals de situatie en klachten was/waren voor aanvang van de zuurstoftherapie.

Naam: ……
Geslacht: Man/vrouw
Geboortedatum: ……
Telefoonnummer:……..
In welk ziekenhuis bent u onder behandeling? …….

Deze vragenlijst is opgedeeld in 3 delen. Het 1e deel bevat een aantal algemene vragen. Het 2e deel bevat vragen over de clusterhoofdpijn. Tussen de vragen door zult u wat uitleg vinden over clusterhoofdpijn zelf. Het 3e deel bevat vragen over eventuele beperkingen in het dagelijks leven.

Er zijn drie soorten vragen. Bij de meerkeuze vragen kunt u één rondje (0) aankruisen met het juiste antwoord, zo nodig kunt u op de stippellijn uw antwoord nog aanvullen. Bij de vragen waar 'Ja/Nee' of 'helemaal/veel/weinig/niets' achter staat kunt u omcirkelen wat voor u van toepassing is. Bij de open vragen wordt u verzocht in uw eigen woorden een korte omschrijving te geven.

Deel 1: Algemene gegevens

1. Wat is uw leeftijd? …….. jaar

2. Wat zijn uw lengte en gewicht?
   Lengte: …….. cm
   Gewicht: …… kg

3. Welke opleiding(en) heeft u gedaan?
   ……...

4. Wat is uw beroep? ……

5. Rookt u?
   Ja/Nee *(Indien nee ga verder naar vraag 9)*

6. Op welke leeftijd bent u begonnen met roken? ……..

7. Hoe lang rookt u nu? …….. jaar

8. Hoeveel sigaretten rookt u nu gemiddeld per dag? …….

9. Heeft u in het verleden gerookt?
   Ja/Nee *(Indien nee ga verder naar vraag 13)*

10. Op welke leeftijd bent u begonnen met roken? ……..

11. Hoelang heeft u gerookt? ……

12. Hoeveel sigaretten heeft u in het verleden gemiddeld per dag gerookt? ….……..

13. Gebruikt u alcohol?
    Ja/Nee *(Indien nee ga verder naar vraag 16)*

14. Hoeveel dagen per week drinkt u alcohol bevattende dranken? ……..

15. Hoeveel glazen alcoholbevattende drank gebruikt u gemiddeld in één week? ……..….

16. Heeft u in het verleden alcohol gebruikt?
    Ja/Nee *(indien nee ga verder naar vraag 18)*

17. Hoeveel glazen alcoholbevattende drank gebruikte u in het verleden gemiddeld per week? …….

18. Heeft u nu of in het verleden te maken gehad met onderstaande ziekten/aandoeningen?
    a. Slaapapneu syndroom? Ja/Nee
    b. Andere vormen van hoofdpijn? Ja/Nee
       Zo ja, wie heeft de diagnose gesteld? Uzelf/ huisarts/ anders, namelijk……..
       Had u deze hoofdpijn eerder dan de clusterhoofdpijn? Ja/Nee
    c. Hersenschudding? Ja/Nee

19. Gebruikt u medicijnen voor andere ziekten/aandoeningen dan clusterhoofdpijn? Zo ja, welke medicijnen en voor welke aandoening?

Medicijn	Aandoening
……..	……..
……..	……..
……..	……..

20. Komt er bij u in de familie clusterhoofdpijn voor? Ja/Nee
    Zo ja, bij wie? ……...……

21. Komt er bij u in de familie migraine voor? Ja/Nee
    Zo ja, bij wie? …….……..

<u>Deel 2: Clusterhoofdpijn specifieke gegevens</u>

Tussen de vragen door zult u informatie vinden over en wat precies bedoeld wordt met een clusterhoofdpijnaanval, clusterperiode en piekfase. Later zult u dit terugvinden in de vragen.

Clusterhoofdpijn
Clusterhoofdpijn wordt gekenmerkt door aanvallen van hevige bonzende of stekende éénzijdige hoofdpijn rondom het oog of de slaap. Tijdens de hoofdpijnaanval kunnen andere klachten voorkomen, zoals bijvoorbeeld een rood, tranend oog, neusverstopping, een loopneus of een hangend ooglid.

Vragen:

22. Hoe zou u de hoofdpijn tijdens een aanval omschrijven? *(Graag één antwoord aankruisen, waarmee de aard van de hoofdpijn het <u>best</u> wordt omschreven)*
- o Borend of kloppend
- o Stekend, alsof er messen in het hoofd worden gestoken
- o Het gevoel alsof het oog eruit gedrukt wordt
- o Anders, namelijk ……..

23. Waar zit de pijn? *(Graag één antwoord aankruisen, waarmee de lokatie van de hoofdpijn het <u>best</u> wordt omschreven)*
- o In/achter de ogen
- o Bij de slapen
- o Bij de tanden
- o Anders, namelijk ……..

24. Heeft u pijn altijd aan één zijde van het hoofd? Ja/Nee
   a. Zo ja, welke zijde? ……..

25. Als u hoofdpijn heeft, heeft u dan ook
   a. Roodheid van het oog aan de kant van de hoofdpijn? Ja/Nee
   b. Tranen van het oog aan de kant van de hoofdpijn? Ja/Nee
   c. Een dichtzittende neus aan de kant van de hoofdpijn? Ja/Nee
   d. Een loopneus aan de kant van de hoofdpijn? Ja/Nee
   e. Een hangend ooglid aan de kant van de hoofdpijn? Ja/Nee
   f. Een nauwere pupil aan de kant van de hoofdpijn? Ja/Nee
   g. Misselijkheid en/of braken? Ja/Nee
   h. Last van fel licht? Ja/Nee
   i. Last van hard geluid? Ja/Nee
   j. Bewegingsdrang (waaronder ook niet stil kunnen liggen)? Ja/Nee

26. Op welke leeftijd had u voor de eerste keer een clusterhoofdpijnaanval? …….

27. Hoe ernstig is de pijn gemiddeld als u geen medicatie gebruikt? (kruis één van de onderstaande opties aan)
- o Matig, er wordt geen of enige hinder ondervonden van de hoofdpijn
- o Hevig, de dagelijkse activiteiten kunnen met moeite gedaan worden
- o Ondraaglijk, onmogelijk om met de dagelijkse activiteiten door te gaan

28. Heeft u de hoofdpijn steeds op vaste tijdstippen op de dag? Ja/Nee

29. Zoekt u tijdens een aanval wel eens de koude op?
   Ja/Nee *(indien nee ga verder naar vraag 32)*

30. Op welke manier zoekt u de koude op? …….

31. Hoeveel heeft de koude de pijn doen verbeteren?
   Helemaal/veel/weinig/niets

32. Heeft u ook ’s nachts hoofdpijn?
   Ja/Nee *(indien nee ga verder met vraag 34)*

33. Als u ’s nachts hoofdpijn heeft wat doet u dan? ……

34. Heeft u ooit onderstaande medicijnen voor de hoofdpijn gebruikt?

a. Triptanen zoals sumatriptan (imigran)? Ja/Nee
   Was dit een injectie, neusspray, zetpil of tablet van 50 mg of 100 mg? …….
   Hoeveel heeft dit medicijn de pijn doen verbeteren? Helemaal/veel/weinig/niets

b. Verapamil (isoptin)? Ja/Nee
   Hoeveel heeft dit medicijn de pijn doen verbeteren? Helemaal/veel/weinig/niets

c. Lithium? Ja/Nee
   Hoeveel heeft dit medicijn de pijn doen verbeteren? Helemaal/veel/weinig/niets

d. Methysergide (deseril)? Ja/Nee
   Hoeveel heeft dit medicijn de pijn doen verbeteren? Helemaal/veel/weinig/niets

e. Pizotifeen (sandomigran)? Ja/Nee
   Hoeveel heeft dit medicijn de pijn doen verbeteren? Helemaal/veel/weinig/niets

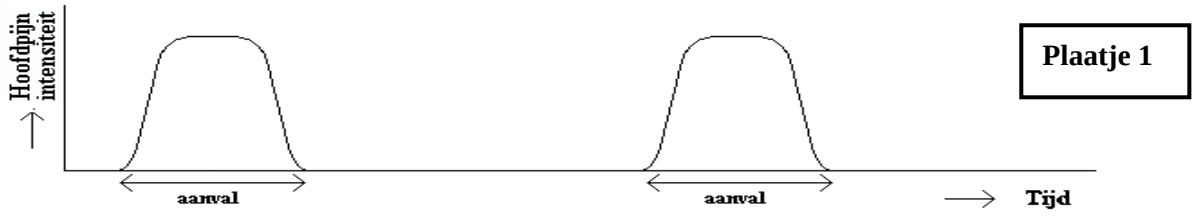
f. Andere medicijnen zoals paracetamol, ibuprofen etc? Ja/Nee
   Zo ja, welke? ……..
   Hoeveel heeft dit medicijn de pijn doen verbeteren? Helemaal/veel/weinig/niets

g. Heeft u ooit eerder zuurstoftherapie gebruikt? Ja/Nee

h. Welke medicatie gebruikt u nu nog voor de hoofdpijn?
   ……..……..

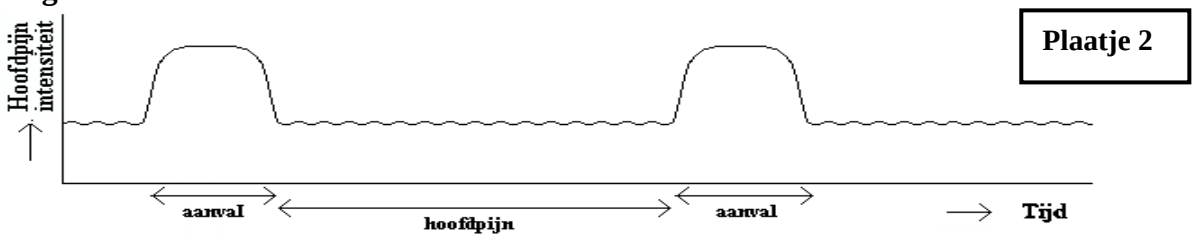
De clusterhoofdpijnaanval

Clusterhoofdpijn komt voor in aanvallen. Een aanval wil zeggen dat de hoofdpijn vrij snel komt opzetten, toeneemt tot een hoogtepunt, enkele minuten, uren of dagen achtereen aanhoudt, en vervolgens weer duidelijk afneemt. De aanvallen zijn dus vrij scherp begrensd. Tussen de aanvallen in is er geen hoofdpijn (zie plaatje 1), of is de hoofdpijn duidelijk verminderd (zie plaatje 2).



Plaatje 1

Vragen:



Plaatje 2

35. Bent u pijnvrij in de periode tussen de aanvallen (plaatje 1) of heeft u tussen de hoofdpijnaanvallen minder hoofdpijn (plaatje 2)?
- o Pijnvrij (plaatje 1)
- o Minder hoofdpijn (plaatje 2)

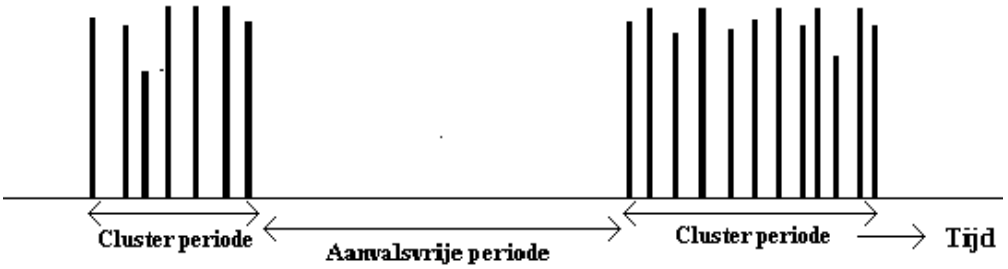
36. Hoe lang duurt een aanval (plaatje 1-2) gemiddeld? (graag één antwoord geven)
- o Korter dan 15 minuten, namelijk……minuten
- o 15 minuten tot 3 uur, namelijk…….minuten
- o Langer dan 3 uur, namelijk ……....uur
- o Weet niet

37. Hoe lang duurt een aanval minimaal?
- o Korter dan 15 minuten, namelijk……minuten
- o 15 minuten tot 3 uur, namelijk ……minuten
- o Langer dan 3 uur, namelijk ……uur
- o Weet niet

38. Hoe lang duurt een aanval maximaal?
- o korter dan 15 minuten, namelijk……minuten
- o 15 minuten tot 3 uur, namelijk ……...minuten
- o langer dan 3 uur, namelijk…….uur
- o weet niet

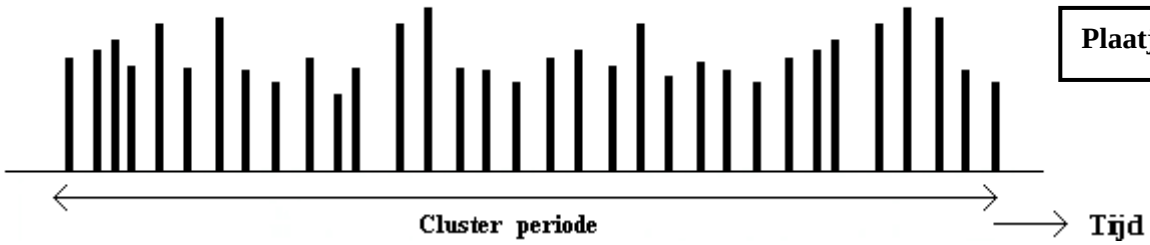
De clusterperiode

Aanvallen van hoofdpijn kunnen in clusterperiodes voorkomen. Een clusterperiode is een periode van enige weken tot enkele maanden, waarin de aanvallen van hoofdpijn zeer frequent voorkomen (soms meerdere malen per dag). Tussen de clusterperiodes zit een aanvalsvrije periode van weken, maanden of zelfs jaren (zie plaatje 3: een verticale streep is een clusterhoofdpijnaanval, de groepen aanvallen is een clusterperiode). Als dit het geval is, spreekt men van episodische clusterhoofdpijn.



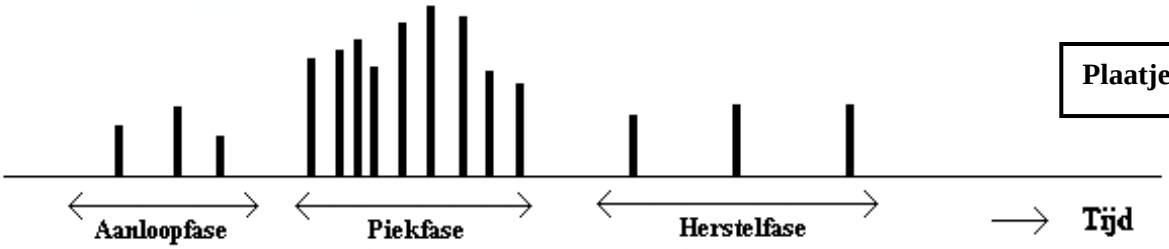
Plaatje 3

Echter, in een klein percentage van de gevallen is er sprake van chronische clusterhoofdpijn. Hierbij treden de aanvallen vrijwel dagelijks of wekelijks op, zonder duidelijke, lange aanvalsvrije perioden (zie plaatje 4).



Plaatje 4

De piekfase van een clusterperiode
De frequentie van aanvallen tijdens een clusterperiode kan verschillen (zie plaatje 5). In de aanloopfase zijn er meestal relatief weinig aanvallen. Vaak wordt de aanloopfase gevolgd door een periode met zeer frequente aanvallen (de piekfase). Deze aanvallen duren vaak langer dan de aanvallen in de aanloopfase. Aan het eind van een clusterperiode nemen de frequentie en de duur van de aanvallen meestal weer af (herstelfase).



Plaatje 5

Vragen:

39. Is dit de 1e keer dat u clusterhoofdpijn heeft?
    - o Ja
      Hoe lang duurt de periode van clusterhoofdpijn tot nu toe? …….
      Ga verder met de vragen 48 t/m 50
    - o Nee

40. Komen de aanvallen van hoofdpijn bij u voor in clusterperiodes met daartussen periodes van weken, maanden of jaren waarin u aanvalsvrij bent (zie plaatje 3)?
    - o Ja *Ga verder met de vragen 41 t/m 50*
    - o Nee (dit betekent dat u geen aanvalsvrije periodes hebt, zie plaatje 4). *Ga verder met de vragen 51 t/m 53*

Vraag 41 t/m 50 zijn bedoeld voor mensen die *wel aanvalsvrije periodes* hebben. Als u geen clusterhoofdpijnvrije episodes heeft, ga dan naar vraag 51.

41. Hoe lang duurt een clusterperiode (plaatje 3) gemiddeld? (graag één antwoord geven)
    - o ……. weken
    - o ……. maanden
    - o ……. jaren

42. Hoe lang duurt een clusterperiode minimaal?
    - o ……. weken
    - o ……. maanden
    - o ……. jaren

43. Hoe lang duurt een clusterperiode maximaal?
- o ……. weken
- o ……. maanden
- o ……. jaren

44. Hoe vaak heeft u een clusterperiode?
- o ……. keer per jaar
- o Eens in de ……. jaar

45. Hoelang duurt een aanvalsvrije periode (plaatje 3, dus de periode tussen twee clusters in) gemiddeld? (graag één antwoord geven)
- o ……. weken
- o ……. maanden
- o ……. jaren

46. Hoe lang duurt een aanvalsvrije periode minimaal?
- o ……. weken
- o ……. maanden
- o ……. jaren

47. Hoe lang duurt een aanvalsvrije periode maximaal?
- o ……. weken
- o ……. maanden
- o ……. jaren

48. Hoe vaak heeft u gemiddeld last van aanvallen van clusterhoofdpijn in de piekfase (zie plaatje 5)? (graag één antwoord geven)
- o ……. keer per dag
- o ……. keer per week

49. Hoe vaak heeft u minimaal last van aanvallen van clusterhoofdpijn in de piekfase?
- o ……. keer per dag
- o ……. keer per week

50. Hoe vaak heeft u maximaal last van aanvallen van clusterhoofdpijn in de piekfase?
- o ……. keer per dag
- o ……. keer per week

Ga verder met de vragen 54 t/m 55

Vraag 51 t/m 53 zijn bedoeld voor mensen die *geen aanvalsvrije periodes* hebben.

51. Hoe vaak hebt u gemiddeld aanvallen? (graag één antwoord geven)
- o ……. keer per dag
- o ……. keer per week
- o ……. keer per maand
- o ……. keer per jaar

52. Hoe vaak hebt u minimaal aanvallen? (graag één antwoord geven)
- o ……. keer per dag
- o ……. keer per week
- o ……. keer per maand
- o ……. keer per jaar

53. Hoe vaak hebt u maximaal aanvallen? (graag één antwoord geven)

- ……. keer per dag
- ……. keer per week
- ……. keer per maand
- ……. keer per jaar

Deel 3: Beperkingen in het dagelijks leven

54. In hoeverre hebben uw lichamelijke gezondheid of emotionele problemen u gehinderd in uw normale omgang met familie, vrienden, buren of bij activiteiten in groepsverband?

Helemaal niet/ enigszins/ nogal/ vrij veel/ ernstig

55. In welke mate bent u door clusterhoofdpijn gehinderd in uw normale werk (zowel werk buitenshuis als huishoudelijk werk)?

Helemaal niet/ klein beetje/ nogal/ vrij veel/ ernstig

Appendix C

Vragenlijst 2: Zuurstoftherapie bij Clusterhoofdpijn
Atrium Medisch Centrum Heerlen, Afdeling Neurologie

Graag invullen na start van de zuurstoftherapie.

Naam: ……
Geslacht: Man / vrouw
Geboortedatum: ……..……..

Net als in de vorige vragenlijst zijn er 3 soorten vragen. Bij de meerkeuze vragen kunt u één rondje (0) aankruisen met het juiste antwoord, zo nodig kunt u op de stippellijn uw antwoord nog aanvullen. Bij de vragen waar 'Ja/Nee' of 'helemaal/veel/weinig/niets' achter staat kunt u omcirkelen wat voor u van toepassing is. Bij de open vragen wordt u verzocht in uw eigen woorden een korte omschrijving te geven.

Vragen:

1. Hoe lang gebruikt u nu de zuurstoftherapie? …….

2. Hoeveel dagen per week heeft u de zuurstof gemiddeld gebruikt?
…….

3. Hoeveel keer per dag heeft u de zuurstof gemiddeld gebruikt?
……..

4. Hoeveel liter zuurstof per minuut gebruikt u (ofwel op welke stand zet u de zuurstof)?
…… liter/minuut

5. Hoeveel minuten na het begin van de hoofdpijnaanval begint u met zuurstof? …… minuten

6. Gebruikte u tijdens de zuurstof ook andere medicatie tegen de hoofdpijn?

A. Gebruikte u sumatriptan (imigran)?
- o Ja
- o Nee

B. Gebruikte u verapamil (isoptin) ter preventie?
- o Ja
- o Nee

C. Gebruikte u andere medicatie voor de hoofdpijn (bv. paracetamol, ibuprofen etc)?
- o Ja, namelijk (geneesmiddel + dosering): ……..
- o Nee

7. Hoeveel verlichting van de pijn kreeg u door de zuurstof (als u geen andere medicatie tegen de hoofdpijn gebruikte)?
Helemaal/veel/weinig/niets

8. Als u de hoofdpijn een cijfer zou moeten geven van 0 tot 10, waarbij 0 helemaal geen pijn is en 10 de ergste pijn is die u zich kan voorstellen, welk cijfer zou u de hoofdpijn vóór gebruik van de zuurstoftherapie geven en na gebruik van de zuurstof? Omcirkel het juiste cijfer.

Cijfer vóór gebruik van de zuurstofbehandeling	1	2	3	4	5	6	7	8	9	10
Cijfer na gebruik van de zuurstofbehandeling	1	2	3	4	5	6	7	8	9	10

9. Hoelang gebruikte u gemiddeld de zuurstof tijdens een hoofdpijnaanval? …….. minuten

10. Na hoeveel tijd aan de zuurstof voelde u gemiddeld verlichting?
- …….. minuten
- …….. uur

11. Na hoeveel tijd aan de zuurstof was de hoofdpijn over?
- …….. minuten
- …….. uur

12. Werkte de zuurstoftherapie bij alle hoofdpijnaanvallen?
- (Vrijwel) alle aanvallen
- Bij meer dan de helft van de aanvallen
- Bij minder dan de helft van de aanvallen
- Bij (bijna) geen aanval

13. Is de frequentie van hoofdpijnaanvallen (dus het aantal hoofdpijnaanvallen per dag of per week) verminderd of juist toegenomen met het gebruik van de zuurstoftherapie?
- De frequentie is afgenomen
- De frequentie is toegenomen
- Er is geen verschil in frequentie van aanvallen

14. Als u zou moeten kiezen: over het algemeen een goede of slechte reactie op zuurstof?
Goed/Slecht

15. Indien u geen gebruikt maakt van de zuurstof, waarom niet?
…….

16. Heeft u nog opmerkingen over de zuurstoftherapie?
…….

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