Chapter 1

Introduction

Headache is a common complaint across the world as two-thirds of people indicate to suffer headaches frequently [1]. Chronic tension-type headache (CTTH) is a form of headache characterised by a bilateral tightening headache with a frequency of more than 15 days per month. CTTH has a point prevalence of 2-5% in the general population with a male/female ratio of 4/5. CTTH can lead to psychosocial problems (distress) and an overuse of pain medication [1,2,3,4].
In Denmark, sickness absence from work because of CTTH has been estimated to contribute 10% to total work absenteeism [5]. The direct annual health care costs resulting from CTTH, and indirect costs due to loss of productivity resulting from CTTH are not clear, but contribute to an estimated total annual cost of 1.6 billion Euros for headache disorders in the Netherlands [6]. In order to decrease the personal discomfort for patients as well as the substantial cost implications for the society-at-large, it is imperative to develop and implement effective treatment strategies for CTTH.

Classification of headache and definition of CTTH

In the second edition of the International Classification of Headache Disorders (ICHD-II) of the International Headache Society (IHS) [7], headache is classified as either a primary or a secondary form of headache, depending on the cause, frequency, duration, location and nature of the headache. In addition to these two forms of headaches, the IHS classifies 'cranial neuralgia' and central or peripheral causes of facial pain. The most frequent forms of primary headache are: tension-type headache, migraine, and cluster headache. The average global one year prevalence of these forms of headaches in the general population, has been estimated at 42%, 11% and 0.2-0.3% respectively [1]. Secondary forms of headaches result from other diseases (tumour, haemorrhage or trauma), or overuse of pain medication (analgesics, non-steroidal anti-inflammatory drugs (NSAID) and triptans) or substances (e.g. caffeine).
Tension-type headache is located on both sides of the head and varies in duration from minutes to days. The intensity of the headache is mild to moderate and does not aggravate with increased routine physical activities, like climbing stairs. Tension-type headache can be sub-divided depending on the frequency of occurrence of headache into episodic tension-type headache (10 to 180 headache days per year) or CTTH, which is when the headache occurs on more than 15 days per month, over a period of 3 months or more longer. In addition

to the previously mentioned characteristics, CTTH can be accompanied by one of the following phenomena: photophobia or phonophobia or mild nausea.

Aetiology of CTTH

While stress is a known predisposing factor to tension-type headache, alcohol consumption, smoking, and being overweight do not appear to contribute to its onset [8,9]. It is not clear how tension-type headache becomes 'chronic'. Although various authors point at a link between CTTH and increasing psychological distress, and a predisposition to depression and anxiety disorders, it is unclear whether these actually constitute risk factors to developing CTTH [9,10].

The term tension-type headache is usually recognisable and tangible for the patient: tension-type headache is accompanied by a hypersensitivity of pericranial and suboccipital muscles, which patients can feel as tension [11]. In cases of CTTH, it is possible to provoke the recognisable headache from myofascial structures in the upper cervical spine [12,13]. The pathophysiological explanation for this 'referred pain' is that nociceptive afferent signals from myofascial structures of the upper cervical spine connect to the interneurons in the spinal dorsal horn of the trigeminal nucleus pars caudalis. Because afferent information from the trigeminal nerve also enters at this level of the dorsal horn, it is possible that through convergence of stimulation of the interneurons via the sensory neurons and cerebral cortex, referred pain can be experienced in the parietal, temporal and frontal areas of the head.

The aetiology, perpetuation and reduction of CTTH is explained by the pathophysiological model of peripheral and central sensitisation. Peripheral sensitisation is a continuously increased sensitivity of peripheral afferent nerve endings in the upper cervical myofascial structures. As a result of peripheral sensitisation, the nocisensory input increases to the trigeminal nucleus pars caudalis located in the cervical spine. Signs for the presence of peripheral sensitisation in CTTH are found in increased pressure sensitivity and presence of active trigger points in the suboccipital musculature of CTTH on headache free days [11]. Local signs of inflammation in trigger points of the suboccipital muscles can contribute to a constantly increased nocisensory activity [14]. If the interneurons, located in the trigeminal nucleus pars caudalis in the dorsal horn,

also display a consistently increased sensitivity, this is defined as central sensitisation.

Central sensitisation is assumed to result in CTTH through an increased sensitivity of interneurons (i) on spinal level (spinal dorsal horn, trigeminal nucleus pars caudalis), (ii) on supraspinal level (thalamus) or (iii) decreased anti-nociceptive activity from supraspinal structures [15]. When an increased sensitivity of interneurons occurs, low threshold sensory input from mechanoreceptors localised in myofascial structures becomes capable of stimulating these interneurons and activate the pain circuit [16]. Central sensitisation in CTTH has been demonstrated by several studies where hypersensitivity is found on administration of thermal, electrical and pressure stimuli and intramuscular noxic substances. This hypersensitivity is also observed during headache free moments, in different tissues (skin, muscle, tendon and nerve structures) and both in the cephalic as in the extra-cephalic region. It is therefore possible that also in the extra-cephalic areas an increase of sensory irritation (hyperalgesia) can be experienced in patients with CTTH [17,18]. An indication of the presence of central sensitisation on the somatosensory cortex is found in a significantly different reduction of electro-encephalographic potentials in favour of healthy subjects compared with subjects with CTTH after induced pain in the trapezius muscle [19].

CTTH treatment in primary health care

In Dutch General Practice, headache is the second most frequently reported complaint [20]. The GP treats headache according to the national guideline for the management of headache of the Dutch College of GPs [21]. The guideline advise GPs to explain to patients with CTTH that there is increased sensitivity of the cranial muscles and that maintaining a healthy balance between the stress patients experience and what they can effectively deal with, can have a beneficial effect on their headache. The guideline recommends to reassure patients with CTTH and to discuss changes in lifestyle. Furthermore, the GP can provide the patient with a nationally produced information leaflet about headache and inform the patient about the existence of a patient headache association. When drug treatment is indicated, paracetamol would be recommended in first instance and NSAIDs secondly. Amitriptyline is effective in reducing frequency of headache in patients with CTTH. Considering non-pharmacological treatments, this national

guideline advises caution with regard to treatments such as neck manipulation; stress management; autogenous training; physiotherapy and acupuncture, as the results from research into the effectiveness of these treatments are ambiguous.

Although manual therapy is not recommended in the national GP guideline, in practice manual therapists regularly treat patients with headache. The patient may be directly referred for treatment of headache complaints, but headache is also indirectly treated in patients with non-specific neck pain: 69% of patients with neck pain also experience headache [22]. At present there are no Dutch national guidelines for the management of headache for manual therapists, neither from the Dutch Association for Manual Therapy nor from the Royal Society for Physical Therapy.

Insufficient evidence of effectiveness of physical therapy for CTTH

Two systematic reviews of the use of physiotherapy and spinal manipulation for tension-type headache reported similar findings regarding the methodological quality of the studies included. According to the authors of these systematic reviews, it is not possible to draw conclusions regarding the effectiveness of physiotherapy and manipulation with tension-type headache because of the small number of studies, the differences in inclusion criteria, heterogeneity of treatments and the lack of an adequate follow-up [23,24]. The reviews included two randomised clinical trials on the effectiveness of manual therapy for CTTH [25,26]. The study by Boline et al. (n = 150) demonstrated that the results of manipulation (predominantly of the cervical spine by using low-amplitude, high-velocity thrust techniques) were no different immediately after treatment compared to results in the control group in which drug treatment (amitriptyline) was prescribed, for all outcome measures: headache frequency, headache intensity, use of pain medication and general well-being. Four weeks after cessation of the treatment period however, manipulation was judged more effective in decreasing headache intensity [25]. In their study (n=30) Demirturk et al. compared the effects of treatment between an experimental group receiving manipulation techniques (Cyriax method) and a control group receiving soft tissue mobilisation of the cervical spine. They did not find significant differences between the groups, immediately after treatment and after 4 weeks follow-up, for any of the outcome measures: headache index (frequency

headache days x headache intensity), mobility of the cervical spine and pressure algometry of the neck muscles [26].

Justification of a trial to investigate the effectiveness of manual therapy for CTTH

Over the last decades, research has investigated the relationship between functional disorders of the cervical spine and chronic headache [27,28,29,30,31,32,33,34,35]. In comparison to healthy subjects and patients with other forms of headaches, such as migraine and episodic tension-type headache, patients with CTTH show a reduction in mobility of the cervical spine [32,35], increased forward head posture [27,32,33,35], trigger points in the cervical musculature [29,31,35], and reduction of isometric muscle strength of the neck flexors [27,28,33]. Manual therapy could be beneficial as it is hypothesised that stabilising the afferent stimuli from mechanoreceptors in the cervical spine by improving cranio-cervical musculoskeletal function (through mobilisation of the cervical spine, training of neck flexor endurance and correction of head posture) will modify peripheral or central sensitisation. This would ultimately lead to a reduction in headache intensity and frequency.

We therefore developed a protocol for a manual therapy multimodal treatment for patients with CTTH. The treatment protocol consists of 3 components: 1) mobilisation of the cervical and thoracic spine, 2) isometric muscle training of neck flexors and 3) exercises and advice on posture. A pragmatic randomised controlled trial (RCT) was subsequently designed to evaluate the effectiveness of the treatment protocol for patients with CTTH in primary care, in comparison to the usual care provided by the general practitioner. We explored the working mechanisms of this manual therapy protocol in order to assess to what extent the different components of the manual therapy protocol contributed to the effect of manual therapy on headache.

Patients who had a strong preference for the manual therapy intervention and could not be randomised participated in a parallel cohort-study. Data from both studies (RCT and cohort) were analysed in the following studies.

In a subsequent study we investigated the course of signs and symptoms in patients with CTTH after manual therapy who participated in the RCT or cohort, and also considered what patient characteristics seemed indicative of a better response to manual therapeutic treatment. This information can be helpful when

advising patients about their options for treatment. To evaluate changes following treatment in headache patients, a simple, short and headache specific questionnaire, the Headache Impact Test 6 (HIT 6), could be useful for clinicians. As the interpretation of the difference in score between baseline and after treatment is crucial, we aimed to determine the minimal clinical important change score on the HIT 6 of all patients (RCT and cohort): a score that distinguishes 'recovered' from 'not recovered' patients in patients with CTTH.

This thesis sets out the results of the research into the effectiveness, mechanisms and prognostic factors of manual therapy for CTTH.

The aims and objectives of this research are:

- ✓ to describe the design of a pragmatic randomised controlled trial of the effectiveness of manual therapy for patients with CTTH and to provide details on the manual therapy treatment protocol (Chapter 2)
- ✓ to investigate the effectiveness of manual therapy compared to the usual care provided by the general practitioner (Chapter 3)
- ✓ to explore the working mechanism of manual therapy in reduction of headache days (Chapter 4)
- ✓ to describe the course of symptoms in patients with CTTH and develop a prognostic model for predicting recovery following manual therapy (Chapter 5)
- ✓ to determine the minimal clinical important change on the Headache Impact Test 6 (HIT-6) for patients with CTTH (Chapter 6)

Chapter 2 describes the design and a pilot study of a pragmatic RCT and provides details on the manual therapy treatment protocol. Publication of the trial design is important to ensure that the results of all trials become available and also reduces the risk of publication bias: in that studies (especially with small sample sizes) reporting positive results are more likely to be published than studies with negative or indeterminate results. Furthermore it offers an opportunity to reflect critically on the study design, independently of the results. To improve the methodological quality of research into the effectiveness of manual therapy for headaches, we followed guidelines for experimental studies in headache [36] and took into account recommendations of systematic reviews

regarding the inclusion criteria for CTTH, an adequate sample size and follow up period [22,23].

Chapter 3 reports the results of the pragmatic RCT conducted in primary care patients with CTTH. The chapter describes the differences between the manual therapy group and the usual care group, in changes on the primary outcome measures (frequency of the number of headache days/2weeks and the use of pain medication) and secondary outcome measures (intensity of headache, cervical spine function, psychosocial factors), which were assessed after two months of treatment and after 26 weeks.

Chapter 4 answers the question which of the three components of the manual treatment protocol (mobilisation of the cervical spine, or isometric training of neck flexors, or posture correction) may contribute to the treatment effect of manual therapy in CTTH. To address this question mediation analysis has been carried out using data of participants from the RCT and from an observational prospective cohort of similar patients who have not consented to randomisation. Mediation analysis tries to identify and explicate the mechanism that underlies the observed relationship between manual therapy and the primary outcome (reduction in headache days) by investigating the influence of a mediator (cervical range of motion or neck flexor endurance or forward head posture).

Chapter 5 describes the course of CTTH symptoms after manual therapeutic treatment and investigates which baseline patient characteristics predict recovery after manual therapy. Data from participants of the prospective cohort study were analysed at 8 and 26 weeks. In this research, recovery following treatment was based on global improvement as perceived by the patient and $\geq$ 50% reduction in headache days.

Chapter 6 considers the minimum change in score on the HIT-6 that can be qualified as a clinically important change and may be used when evaluating the outcome of treatment. The HIT-6 is a frequently used, easy to administer questionnaire that consists of 6 questions pertaining to headache. The HIT-6 was used with all participants of both studies (RCT and cohort study).

In **chapter 7** the main findings of the research are summarised and the implications of the research discussed. Recommendations for clinical practice and further research are set out.

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