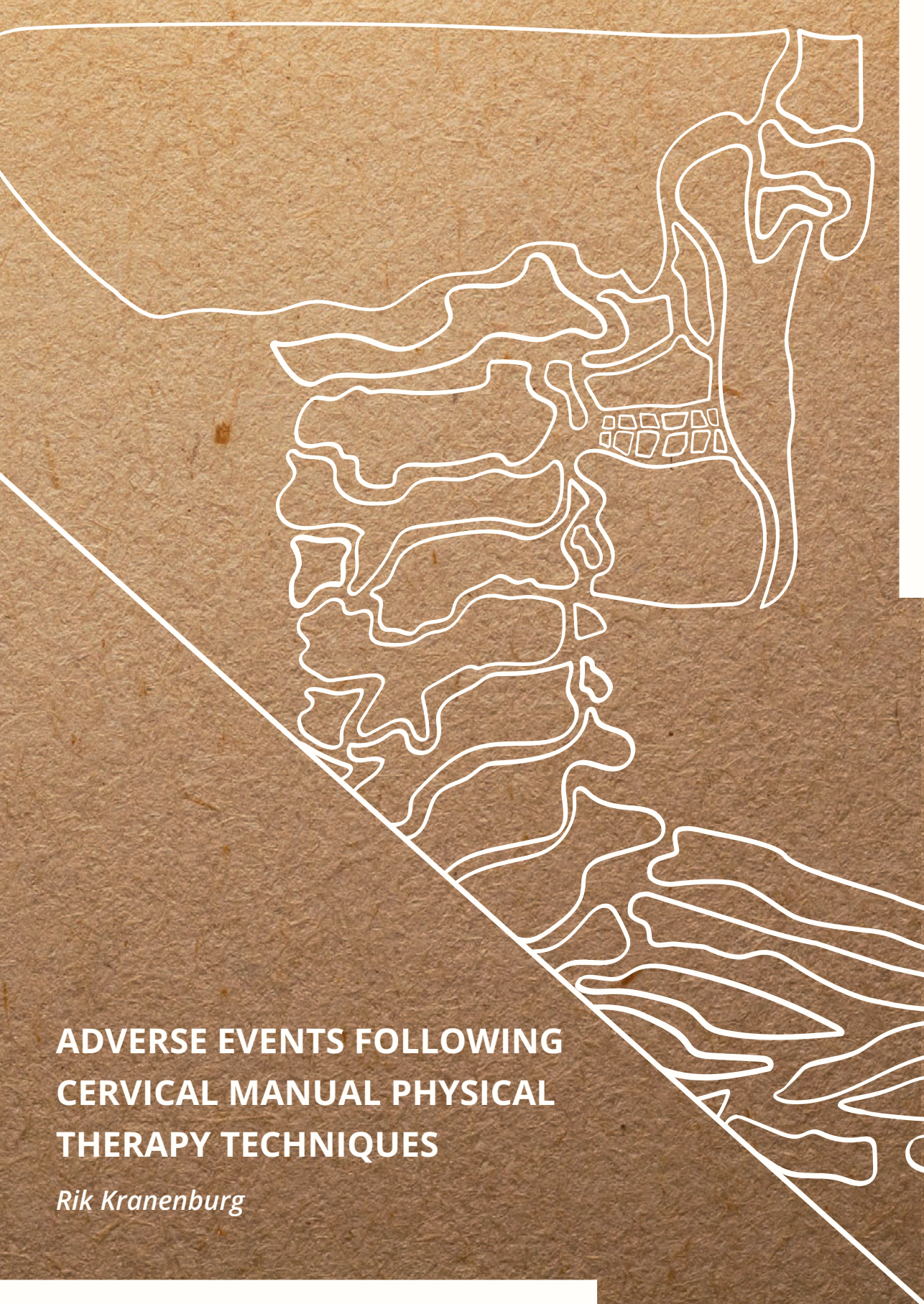

ADVERSE EVENTS FOLLOWING CERVICAL MANUAL PHYSICAL THERAPY TECHNIQUES

Rik Kranenburg

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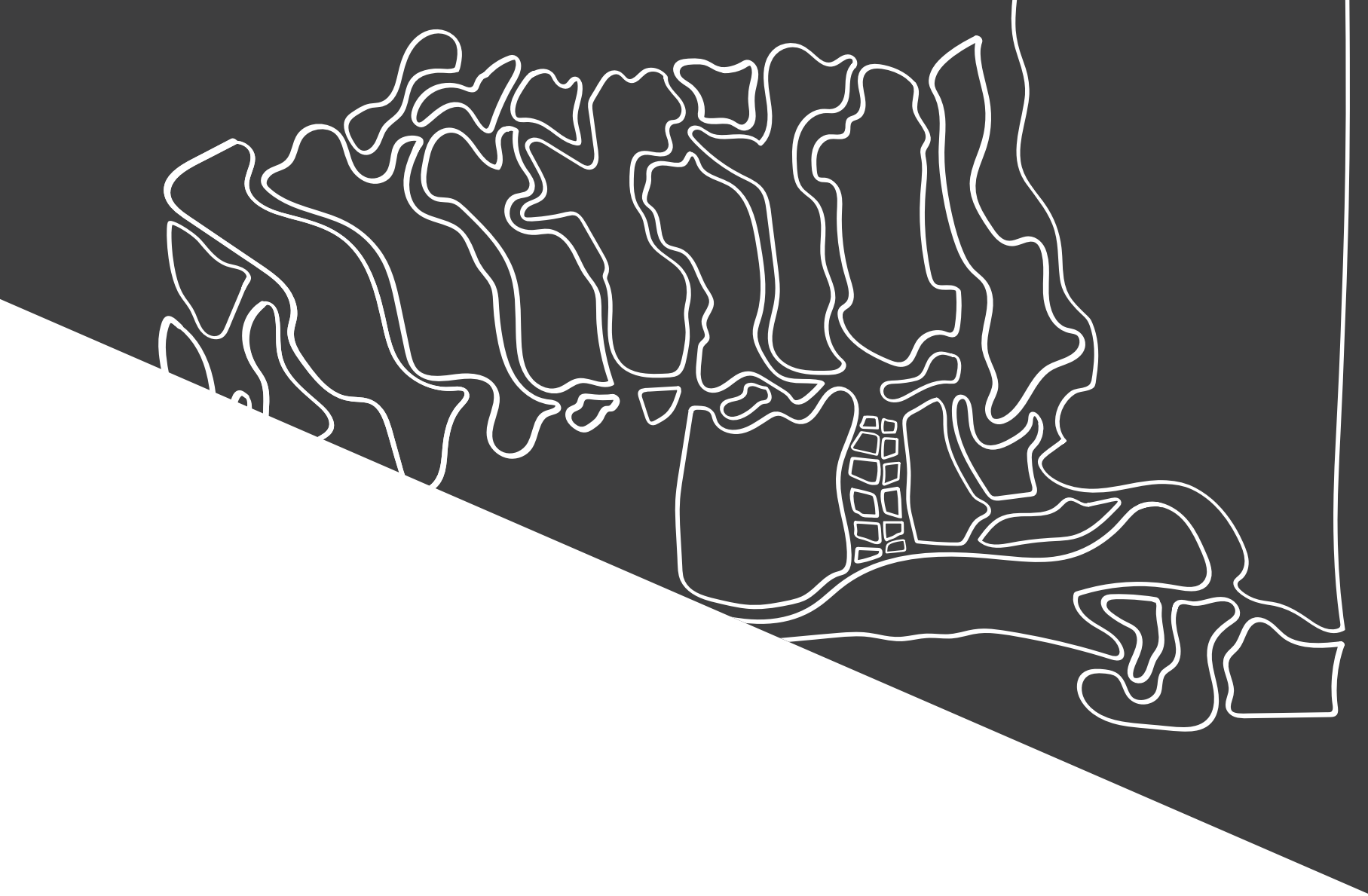
CONTENTS

		Page
Chapter 1	General introduction	**8**
Chapter 2	Beliefs and the use of spinal thrust joint manipulation: a survey of Dutch manual physical therapists *Submitted*	**22**
Chapter 3	Adverse events following cervical manipulative therapy: consensus on classification among Dutch medical specialists, manual therapists, and patients *Published in: Journal of Manual and Manipulative Therapy, 2017; 25;(5);279-287*	**42**
Chapter 4	Adverse events associated with the use of cervical spine manipulation or mobilization and patient characteristics: A systematic review *Published in: Manual Therapy, 2017; 28; 32-38*	**72**
	Response letter to: Adverse events associated with the use of cervical spine manipulation or mobilization and patient characteristics: A systematic review *Published in: Musculoskeletal Science and Practice, 2018; 30; e95*	**112**
Chapter 5	Carotid and vertebral arterial dissections after manual physical therapy: a case control study *Submitted*	**116**
Chapter 6	Effects of head and neck positions on blood flow in the vertebral, internal carotid, and intracranial arteries: A systematic review *Published in: JOSPT, 2019; 5; 1-59*	**132**
Chapter 7	Adverse events after cervical manipulative therapy: A prospective cohort study *Submitted*	**184**
Chapter 8	Summary	**204**
	General discussion	**209**
	Nederlandse samenvatting	**212**
	Dankwoord	**217**
	Research Institute SHARE	**220**



GENERAL INTRODUCTION

1

INTRODUCTION

Manual physical therapy is considered an effective intervention for non-specific neck pain and neck-related headache. However, there is a debate in literature and amongst clinicians about the use of these therapeutic interventions in relation to the risk of complications following manual physical therapy. Within the process of clinical reasoning, manual physical therapists (and other professionals who apply manual therapy intervention to the cervical spine) should weigh the expected benefit of the interventions in an individual patient against the risk of adverse events, the so-called risk-benefit ratio. Considerations of the risk-benefit ratio should be based on the knowledge of the effectiveness of these interventions, and on the risk and frequency of occurrence, also known as the incidence, of adverse events following these interventions. Until now, there has been a lack of information about the incidence and characteristics of adverse events following manual physical therapy (and comparable interventions) applied to the cervical spine.

This introduction to the thesis will focus on the determinants of the risk-benefit ratio related to manual physical therapy interventions applied to the cervical and upper cervical spine. An oversight of literature concerning the characteristics of non-specific neck pain (and related headache), the epidemiology of non-specific neck pain (and related headache), and the effects of manual physical therapy will be described. Thereby, current knowledge of the characteristics and frequency of occurrence of adverse events (which knowledge is scarce) will be given. As manual physical therapy interventions are described in relation to adverse events, characteristics of these interventions are described too.

CHARACTERISTICS AND CLASSIFICATION OF NON-SPECIFIC NECK PAIN

Neck pain is a common and multimodal health problem that includes physical, affective, cognitive, and social aspects.(Blanpied et al., 2017; Hoy et al., 2014) Usually the cause of the neck pain is benign (99%).(Rubinstein et al., 2008) The patho-anatomical basis for neck pain is unknown in most patients and therefore characterized as nonspecific or mechanical.(de Vries et al., 2016) The most common used categories for neck pain are: 1] neck pain with mobility deficits; 2] with impaired movement coordination; 3] neck pain with headache; 4] neck pain with radiating pain; and 5] neck pain and migraine.(Blanpied et al., 2017; Gross et al., 2015; Hogg-Johnson et al., 2008; Jull and Hall, 2018) The exact relationship between neck pain and headache is unknown. However, the prevalence of neck pain is significantly higher in patients with migraine (76.2%) and tension type headache (88.4%) than in the general population (57.8%).(Ashina et al., 2015; Moore et al., 2017) The most

used classifications for neck pain are by time, severity, symptoms or anatomical structures.(Bier et al., 2018; Blanpied et al., 2017; Guzman et al., 2009)

EPIDEMIOLOGY OF NON-SPECIFIC NECK PAIN

The incidence of neck pain is estimated varying from 14%-21%%, a point prevalence of 4.9%, and a 1 year prevalence ranging of 37.5%.(Blanpied et al., 2017; Fejer et al., 2006; Hoy et al., 2014) With a 4th place for disability on the musculoskeletal burden of disease, the influence on daily life can be considered as severe.(Smith et al., 2014) In the Netherlands, It is the third musculoskeletal location for complaints and 40% of the total costs of spinal pain are thought to be due to neck pain.(Bier et al., 2018; Picavet and Schouten, 2003)

CHARACTERISTICS OF MANUAL PHYSICAL THERAPY INTERVENTIONS

Both neck pain and headache patients frequently seek help in primary care for a diagnosis and to relieve symptoms.(Blanpied et al., 2017; Gross et al., 2015; Moore et al., 2017) Treatments are often multimodal during which both hands-on and hands-off techniques are advised and used.(Bier et al., 2018; Blanpied et al., 2017) Hands-off techniques may consist of specific or general exercises, advice, postural corrections, cognitive behavioural therapy, and workplace interventions. Hands-on therapy may consist of cervical mobilizations, manipulations, neurodynamics, taping and massage therapy. Most of the advised techniques are based on low quality evidence. However, the combination of cervical mobilizations or manipulations and exercise therapy for neck pain patients Grade I or II is based on high quality evidence.(Bier et al., 2018; Blanpied et al., 2017)

Manipulations and mobilizations are both hands-on techniques. Although the terms might seem alike, they are interchanged in literature and are often deployed for the same indications or outcomes, they are significantly different.(Mintken et al., 2008; Rushton et al., 2016, p. 31) In their educational standards document, the International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) has defined a manipulation as: "*A passive, high velocity, low amplitude thrust applied to a joint complex within its anatomical limit with the intent to restore optimal motion, function, and/or to reduce pain.*" Following the same document a mobilization is defined as: "*A manual therapy technique comprising a continuum of skilled passive movements that are applied at varying speeds and amplitudes to joints, muscles or nerves with the intent to restore optimal motion, function, and/or to reduce pain.*"(Rushton et al., 2016, pp. 31–32) The key difference between those two techniques is the high velocity impulse with which a manipulation is applied. Furthermore, a manipulation is applied towards the end

of the anatomical limit of a joint, whereas a mobilization can be applied in an end range position as well as in the range before that anatomical limit.

BENEFITS OF MANUAL PHYSICAL THERAPY

The possible benefits of treatment modalities which are weighed against the possible risks are an essential component of the complex and multimodal clinical reasoning process of a manual physical therapist.(Rushton et al., 2016) Cervical manipulations seem more effective for neck pain than thoracic manipulations and demonstrated fewer side effects.(Puentedura et al., 2011) The effectiveness of cervical techniques, including manipulations and mobilizations, has been described in a Cochrane review.(Gross et al., 2015) This review, including 51 trials with 2920 participants, showed that manipulations seemed not to be more effective than mobilizations at an immediate, short term and intermediate follow-up. However, multiple sessions with cervical manipulations led to more pain relief and functional improvement than pain medication at immediate, short, intermediate and long follow-up. Effect sizes described in Standard Mean Differences (SMD) were reported for pain between -0.19 and -0.34 favoring multiple cervical manipulations versus medication. When comparing cervical manipulations versus cervical mobilizations the pooled SMD for pain was -0.07 favoring manipulation and the SMD for function and disability scored between 0.10 and -1.71. Differences in execution of manual techniques could also lead to differences in effectiveness.(Gross et al., 2015) A combination of manual techniques and exercise is recommended.(Bier et al., 2018)

RISKS OF MANUAL PHYSICAL THERAPY

The World Health Organization considers cervical manipulations or mobilizations performed by chiropractors as safe and effective treatment which carries the risk of few mild and transient adverse events.(World Health Organization, 2015) Most of those risks concern minor or moderate adverse events.(Cagnie et al., 2004; Chaibi and Russell, 2019; Sweeney and Doody, 2010) Although it can be hard to classify adverse events, they can be classified as not adverse, minor, moderate and major adverse. (Carnes et al., 2010) 'Major' adverse events are defined as medium to long term, moderate to severe and unacceptable, they normally require further treatment and are serious and distressing; 'Moderate' adverse events are as 'major' adverse events but only moderate in severity; and 'Mild' and 'not adverse' adverse events are short term and mild, non-serious, the patient's function remains intact, and they are transient/reversible; no treatment alterations are required because the consequences are short term and contained.(Carnes et al., 2010) Classification can be difficult without a context or details and there is a possible overlap between

categories in the classification as described by Carnes.(Carnes et al., 2010) In particular, the category 'moderate' is difficult to work with in clinical practice and in research. The overlap between the minor and major categories is probably too large. (Carlesso et al., 2011) Furthermore, if the definitions used to categorize were linked to the international classification of diseases and Related Health Problems (ICD-10) and the international classification of functioning, disability and health (ICF), that would enhance clarity and simplify usage. (World Health Organisation, 2012, 2001)

The incidence of major adverse events following manual therapy is of considerable interest and has only described anecdotally. However, incidences have been estimated ranging from 1:3.000 to 1:6.000.000.(Assendelft et al., 1996; Magarey et al., 2004; Nielsen et al., 2017) However, due to the severity of the consequence's cases are repeatedly published and are abundantly covered by media. In most published cases a cervical manipulation was involved during the treatment session.(Ernst, 2007; Nielsen et al., 2017) The Heath and Youth Care Inspectorate in The Netherlands receives approximately two cases with major AE following manual physical therapy per year.(Pool, 2019) However, the frequency with which manipulations and mobilizations are applied is unknown in The Netherlands. The absence of representable incidence rates makes it difficult to place those adverse events in perspective. Particularly since causality has not been established, discussions remain intense on whether or not to use these techniques and which precautions should be considered.(Cassidy et al., 2012; Church et al., 2016; Wand et al., 2012) To assist the clinician in this clinical reasoning process and physical assessment the IFOMPT has developed a framework which has also generated discussion.(Kerry et al., 2014; Rushton et al., 2014; Scholten-Peeters et al., 2014) Since most of the adverse events following cervical manipulations seem of a neurovascular origin the framework focusses on cervical artery dysfunctions.(Biller et al., 2014)

CERVICAL ARTERIAL DISSECTION

Cervical arterial dissections arise when the inner wall of an artery (tunica intima) of the outer adventitia layer ruptures and creating a false lumen.(Blum and Yaghi, 2015) This may narrow or even close the lumen of the artery. Also, it can create a secondary blood flow in the false lumen, resulting in a thrombus which can cause a stoke. Cervical arterial dissections can occur in the internal carotid arteries and in the vertebral arteries. (Figure 1) The internal carotid arteries are also known as the anterior circulation because they supply the anterior part of the brain with blood. The vertebral arteries are often referred to as the posterior circulation because the supply the posterior part of the brain with blood. Fortunately, mortality rates of

cervical dissections are low (4%) and functional outcomes are usually good.(Debette, 2014) The pathophysiology of cervical dissection is multifaceted and not yet fully understood.(Debette, 2014; Hutting et al., 2018; Thomas, 2016) The incidence rate for a spontaneous carotid artery dissection is 2.3-3.0 per 100.000 people and for the vertebral artery 1.0-1.3 per 100.000 people and should be taken into account when calculating an increased risk after cervical techniques.(Debette et al., 2009; Dziewas et al., 2003; Schievink et al., 1994) Although no causal relationship between cervical manipulations and cervical dissections has been established, an association has been suggested.(Cassidy et al., 2017, 2008) A cervical artery dissection can be caused by intrinsic and extrinsic factors.(Debette, 2014; Thomas, 2016) Intrinsic factors may be an underlying arterial pathology, anomaly or a genetic predisposition. (Debette et al., 2009; Thomas, 2016) Infections or cervical traumata such as motor vehicle accidents are considered extrinsic factors. It is unlikely that a cervical manipulation will damage a healthy arterial wall. However, in extremely rare cases, when a cervical arterial dissection is already present, it cannot be disregarded that cervical manipulation is such an extrinsic factor.(Eriksen et al., 2011) It has also been suggested that the manipulation may trigger an embolus or a vasospasm or that the manipulative position might alter blood flow.(Haldeman et al., 1999; Mann and Refshauge, 2001; Mitchell, 2009) However, the latter explanation is challenged by the anatomical disposition via the circle of Willis. Furthermore, it would also mean that the technique itself is secondary to the treatment position which is contrary to the reported cases of major adverse events. Moreover, it would be in contrast to the suggestion that mobilizations are often presented as a safer alternative to manipulations.(Gross et al., 2015) Especially since cervical manipulations are typically performed in a mid-range

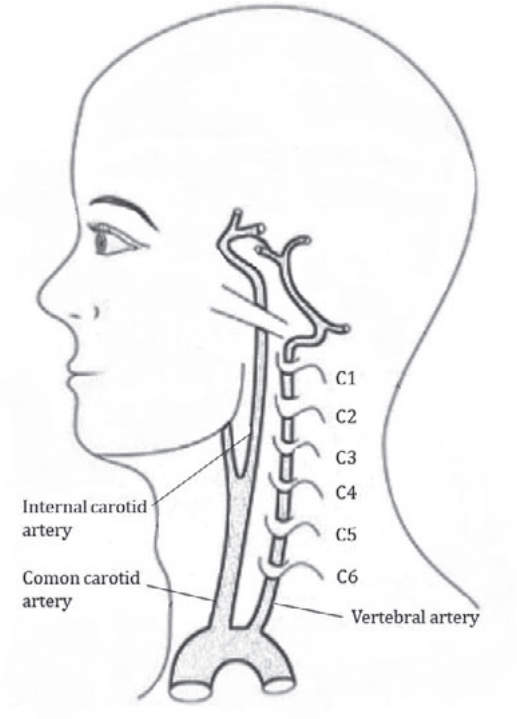


Figure 1. Cervical arteries

position while mobilizations are regularly performed in an end-range position. (Dunning et al., 2016; Reid et al., 2014)

Cervical arterial dissections usually present with local pain, ipsilateral neck pain, ipsilateral headache and a Horner syndrome and this typical pattern is only existent in less than one-third of patients. Diagnosis is regularly overlooked for some time precisely because of the lack of specific signs.(Thanvi et al., 2005) Usually, unilateral neck pain or headache have a musculoskeletal origin and are benign. Unfortunately, these arterial symptoms can mimic the musculoskeletal complaints when other neurological symptoms are absent. Especially, for the carotid artery dissection differentiation can be difficult. (Debette et al., 2009; Thomas, 2016) However, cervical arterial dissection patients frequently label their symptoms as being different to those experienced before or as abnormal.(Debette et al., 2009) Besides an MRI T1 with fat suppression, a comprehensive patient history seems essential to identify patients at risk.(Debette et al., 2009; Puentedura et al., 2012; Rushton et al., 2014; Thomas, 2016) Especially because pre-manipulative arterial tests seem to have a low diagnostic accuracy, a low pretest probability and can even be harmful for the patient.(Hutting et al., 2018, 2013)

AIM OF THIS THESIS

There is a need to gain clarity on patient and treatment characteristics that can predict adverse events following manual physical therapy and data to put the adverse events in perspective. Therefore, the three aims of this thesis are:

1] To identify patients which are more at risk for AE following manual physical therapy by identifying and understanding risk factors within the patient, therapist and the techniques used during treatment.
In **chapter two,** the purpose is to gain a general insight in spinal care in manual physical therapy practices so a perspective can be formed. This will be achieved by quantifying the amount of manipulations per spinal region during treatments in clinic, by determining thoughts of clinicians on safety and efficacy about the application of manipulations and inventory their clinical decision making. The purpose of **chapter four** is to systematically review the literature to identify the characteristics of 1) patients, 2) practitioners, 3) treatment process and 4) adverse events (AE) occurring after cervical manipulation or cervical mobilization. In **chapter five**, the purpose is to explore differences between hospitalized CeAD patients and controls receiving a cervical manipulation in clinical practice by means of a case-control study. The purpose of **chapter six** is to determine, the effects of cranio-

cervical positions and movements on hemodynamic parameters (blood flow velocity and/or volume) of cervical and cranio- cervical arteries.

2] To develop a classification system that is suitable for clinical practice and research by which AE can be reported.
The aim of **chapter three** is to develop a classification system for adverse events that is useful for research and practice, including patients and clinicians' perspectives, has an acceptable number of categories and clear definitions, and is based on the international classification diseases and Related Health Problems (ICD-10) and the international classification of functioning, disability and health (ICF).

3] To collect the frequency with which techniques are used and the frequency with which adverse events are reported to put the AE in perspective.
In **chapter seven**, purpose is to determine the number, type and predictors of AE following cervical treatments performed by Dutch manipulative therapists.

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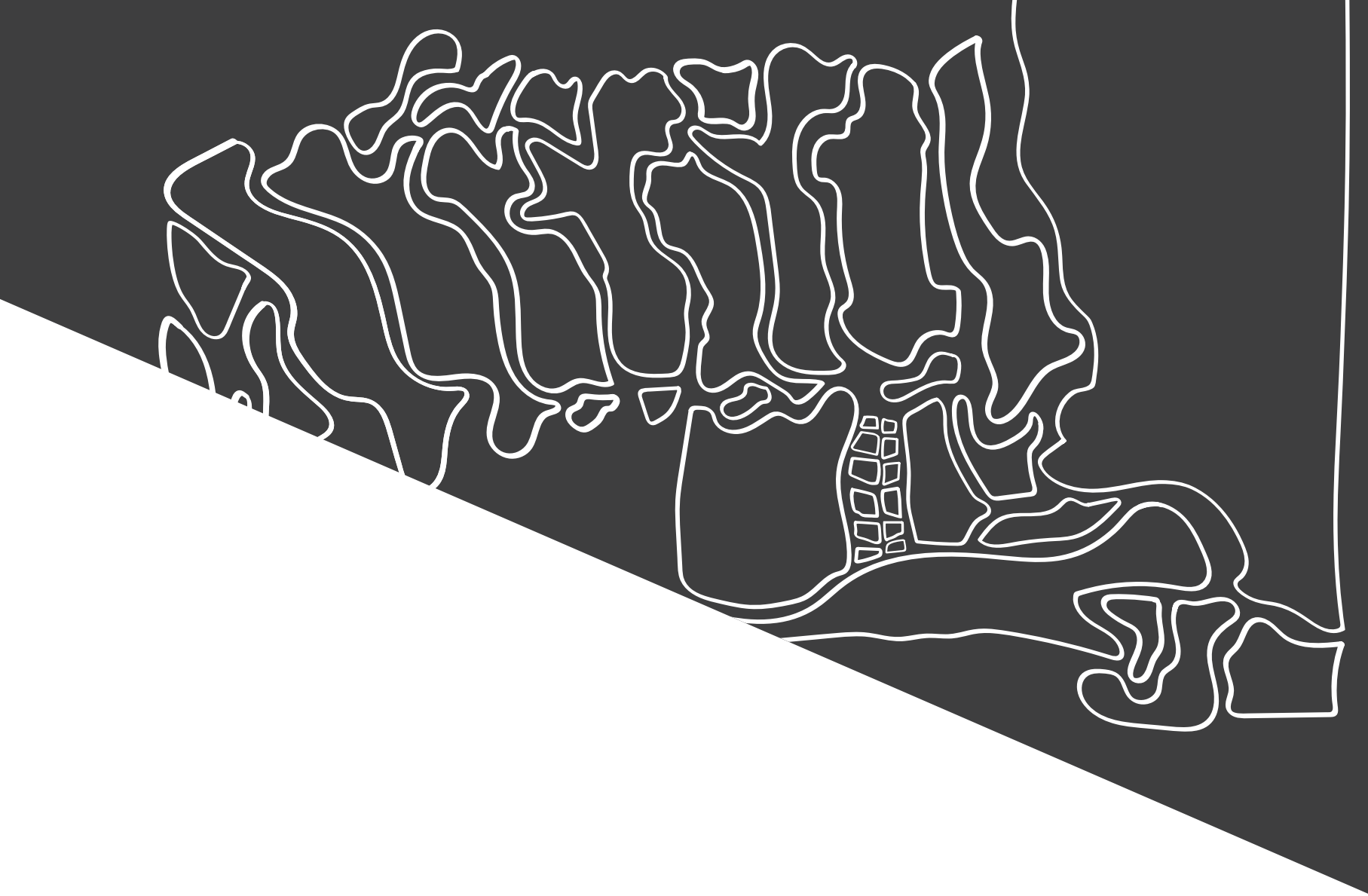

BELIEFS AND THE USE OF SPINAL THRUST JOINT MANIPULATION: A SURVEY OF DUTCH MANUAL PHYSICAL THERAPISTS

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Submitted

ABSTRACT

Introduction: Thrust Joint Manipulation (TJM) is a widely used intervention in spinal care, however there are differences in its use between countries and spinal regions. The aim of this survey study was to quantify the amount of TJM used within the spinal regions among Dutch certified manual physical therapists, their thoughts regarding safety and efficacy related to the application of TJM techniques.

Method: The 19-question e-survey was based on a similar survey in the USA. Since the Netherlands has a separate professional standard for the upper cervical spine, questions enabled differentiation between upper- and mid/lower cervical spine. The survey was launched during a national manual therapy congress and distributed via social media (April-July 2018). Descriptive analysis, MANOVA and qualitatively analyses were used.

Results: From the 211 responses, 150 were male, with a mean age of 44.9 (±11.2), a mean clinical experience of 12.8 years (±9.6) as manual physical therapist, 87% had a master's degree and 97 % worked in a private practice. Except for the upper cervical spine, more than 80% of the participants felt that TJM was safe, were comfortable performing TJM. Overall >80% performs additional screening prior to TJM. Concerns about safety is the greatest barrier for upper cervical TJM.

Discussion: Findings indicate that overall Dutch Manual Therapists believe TJM to be safe and effective and are comfortable performing them, except for the upper cervical spine, where concerns exist regarding safety and acquiring written informed consent.
Level of evidence: 2b

INTRODUCTION

Thrust Joint Manipulation (TJM) is an intervention widely used by manual physical therapists, chiropractors and osteopaths, within a multimodal biopsychosocial approach to manage spinal complaints. TJM techniques are characterized as involving a specific high-velocity low amplitude thrust with the aim of achieving joint cavitation.(Puentedura et al., 2017) Evidence, including clinical guidelines supports TMJ for all spinal regions for improving patient-reported outcomes, and performance-based outcomes.(Bier et al., 2018; Blanpied et al., 2017; Cross et al., 2011; de Campos, 2017; Gross et al., 2015; Michaleff et al., 2012) Although recommended, TJM techniques have been linked with serious adverse events and unwanted side-effects.(Church et al., 2016; Hebert et al., 2015; Kranenburg et al., 2017; Nielsen et al., 2017; Puentedura et al., 2012; Puentedura and O'Grady, 2015; Thoomes-de Graaf et al., 2017) Serious adverse events are mostly reported for the cervical spine and may be major with consequences such as spinal cord injury or stroke, especially related to TJM in the cervical and upper cervical spine.(Cagnie et al., 2004; Puentedura et al., 2012) Unwanted side-effects are more common and involve onset of new symptoms or a temporary worsening of symptoms for only 24 to 48 hours. Adverse events and unwanted side-effects may lead clinicians to limit their use of TJM or perhaps even abandon.(Carlesso et al., 2010; Puentedura et al., 2017)

A recent U.S. survey investigated physical therapist (PT) utilization, comfort and perceptions about TJM.(Puentedura et al., 2017) Pre-thrust examination to prevent adverse events and unwanted side-effects was performed most often in the cervical spine. PT's reported being most comfortable with TJM in the thoracic, less so in the lumbar and least in the cervical spine. Most of the barriers to use TJM in U.S. involved fear / lack of confidence or a lack of education.(Puentedura et al., 2017) Thoracic spine TJM was considered the most safe and effective, followed by the lumbar spine and cervical spine.(Puentedura et al., 2017) PTs appear to be less comfortable and less confident in the cervical spine region whilst it is also the region reported to be most susceptible to adverse events during their training.(Thoomes-de Graaf et al., 2017)

In the Netherlands, clinical practice differs from the U.S in several ways. Firstly, slightly more than 50% of all patients in private practice enter healthcare via direct access.(NIVEL, 2016) Secondly, TJM is not included in the entry-level Bachelor of Physical Therapy program, but is instead, taught in a three-year manual therapy master's program (fulfilling IFOMPT Educational Standards). After this, a Dutch

PT becomes certified as a manual therapist. All certified manual therapists are registered in a quality register. However, there are also non-certified professionals who use TJM techniques having learned such skills in short professional courses. Thirdly, for the application of upper cervical spine (C0-C3) TJM techniques, a professional standard exists. This professional standard was developed by the Dutch Manual Therapy Association and is based on the IFOMPT Cervical Artery Dysfunction Framework.(Rushton et al., 2014) It comprises components of medical history, pre-manipulative examination and written informed consent.(Rushton et al., 2014)

The aim of this survey was to quantify the amount of TJM used within the lumbar, thoracic, mid/ lower cervical (C3-C7) and upper cervical (C0-C3) regions among Dutch certified manual physical therapists, and to determine their thoughts about safety and efficacy related to the application of TJM techniques and their clinical decision making. This study sought to contribute to the discussion concerning safety and efficacy of spinal TJM.

METHODS

A digital survey was developed using the Enalyzer software package specifically for IFOMPT members in the Dutch manual physical therapy setting.("Enalyzer," 2018) Previous surveys' in the U.S. (Puentedura et al., 2017) and U.K. (Heneghan et al., 2018) were used to inform the development of the survey. The study is reported in line with the Checklist for Reporting Results of Internet Surveys (CHERRIES). (Eysenbach, 2004)

SURVEY DEVELOPMENT

The survey of Puentedura et al. (Puentedura et al., 2017) was translated and adapted (HAK) into the Dutch setting with a separate standard for the upper cervical spine. The survey was piloted and revised by two native Dutch expert manual therapists with extensive experience in orthopedic PT education and research (NH and MS). Key differences between the Dutch and U.S. survey related to therapist certifications and differentiation of practice for TJM for the upper (C0-C3) and mid / lower cervical spine (C3-C7) regions.

A brief description of the content and the aim of the survey was provided. Most questions were closed questions with an option for additional text for responses to questions where 'other' was provided. The survey contained questions about gender, age, level of education, other relevant courses, experience as a PT,

experience as a manual therapist, work setting, estimated percentage of patients with complaints for each spinal region, and whether the respondent was aware of any of the clinical prediction rules for TJM. (Questions 1-10) Next, the participants were asked for their opinions on the following areas: 1] beliefs about the safety of TJM for each of the spinal regions (Question 11); 2] pre-thrust examination for each spinal region (Question 12); 3] use of TMJ for each spinal region (Question 13); 4] their level of comfort performing TMJ for each spinal region (Question 14); and 5] possible barriers to performing TJM for each spinal region (Questions 15-18).

Content validity was strengthened using Puentedura's publication and the clinical expert opinions (HAK, MS, NH and NHe.(Puentedura et al., 2017)

The survey was piloted by four Dutch manual therapists who gave feedback on wording, clarification of response choices and the estimated duration.

For all respondents, all questions were presented in the same order and all questions were mandatory for survey completion. If respondents answered that they were not aware of any clinical prediction rules, they were not asked to clarify which ones. For the last four questions respondents could, next to the predefined answers choose an 'other' option in which they could specify barriers.

SETTING AND RECRUITMENT

The link to the survey was presented at the annual national manual therapy conference in the Netherlands on April 7, 2018, posted on the website of the Dutch Association for Manual Therapy (NVMT), distributed via social media (Twitter, Facebook and LinkedIn) and word of mouth. The survey was open until July 31, 2018. To optimize the response rate, reminders were posted on social media and published on the NVMT website and once in the NVMT news mail.

A priori, sample size was calculated using the formula as suggested by Dillman for e-surveys.(Dillman, 2007)

$$Ns = \frac{(Np)(p)(1-p)}{(Np-1)(\frac{B}{C})^2 + (p)(1-p)}$$

In this formula, Ns = completed sample size for desired level of precision, Np = size of population, p = proportion of population expected to choose one of the two

response categories, B = acceptable amount of sampling error, C = Z statistic associated with the confidence level.

For this study, the number of registered MPT's fulfilling the IFOMPT educational standards in Netherlands was 4500 as of October 2018.(Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF), 2018) The proportion of the population (p) expected to choose one of the two response categories (to participate or not) was set at 50/50 or 0.5. For the sampling error, 0.05 was set as acceptable with a confidence level of 90% and a corresponding Z-statistics of 1.645. This resulted in a required sample size (Ns) of 256 persons.

DATA PROCESSING AND ANALYSIS

Data of completed surveys was exported to Microsoft Excel (2016) and imported to IBM SPSS version 23 for statistical analysis. For the demographic data, descriptive analyses (frequencies, mean and standard deviation (SD)) were used. Frequencies and percentages are presented for closed questions, in tables or graphical bars. The four statements that surveyed the beliefs about TJM were analyzed with a related samples Friedman's two-way analysis of variance by ranks, to explore the differences in thoughts about safety and effectiveness across spinal level. The level of significance was set at <0.05. Significant values were adjusted by the Bonferroni correction for multiple tests. The four statements were analyzed for differences in clinical experience using MANOVA. The open answers were analyzed qualitatively in order to look for specific 'themes' in barriers for each of the spinal regions. This was done by a posterior content analyses for 'themes' to be identified and quantified with calculation of frequencies for each category by 2 researchers (HAK and MS). (Vaismoradi et al., 2013)

ETHICS

This study was deemed exempt by the Medical Ethical Committee of the University Medical Center Groningen, The Netherlands. At the start of the survey participants were informed that participation was voluntarily, and continuation assumed an informed consent. Participants were informed regarding the aim of the survey, the expected duration and assurance of participant anonymity.

RESULTS

In total, the survey was accessed 309 times, with 211 surveys completed, (68% (211 / 309)). A further 97 incomplete surveys were not included in the final analysis

as inclusion of returns with missing data would introduce bias and affect overall findings.(Eysenbach, 2004)

DEMOGRAPHICS

Of the 211 complete responses, 150 were male (71.1%) with a mean age of 44.9 (SD11.2, range 26-67). The 61 participating females had a mean age of 39.4 (SD9.9, range 26-63). Details of ages, years of practice and level of education, and work setting are specified in Table 1.

ESTIMATED PERCENTAGE OF PATIENTS FOR EACH SPINAL REGION

To put the participants answers into perspective, they were asked to estimate the percentage of patients in their clinic for each spinal region. Patients with cervical complaints are seen most often (36%), followed by the lumbar region (35%), the thoracic spine (18%) and the pelvic region (11%).

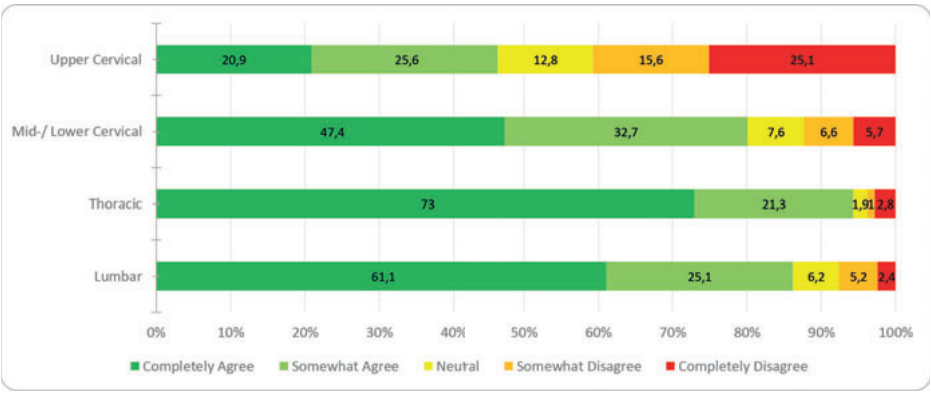
AWARENESS OF CLINICAL PREDICTION RULES

Most respondents (80.6%) were aware of spinal clinical prediction rules related to TJM. Of the respondents that answered affirmative, 143 (84%) respondents knew clinical prediction rules about low back pain and lumbar manipulation; 121 (71.2%) respondents knew about the clinical prediction rules concerning neck pain and thoracic manipulation; and 142 (83.5%) knew about clinical prediction rules for neck pain and cervical manipulation.

UTILIZATION OF TJM

Friedman's showed a significant difference between the regions. $x^2(3) = 285.268$, $p < 0.000$. Post hoc tests illustrated a significant difference between upper cervical and lumbar ($p = 0.000$), upper cervical and thoracic ($p = 0.000$), upper cervical and mid/ low cervical ($p = 0.000$), mid/ low cervical and thoracic ($p = 0.000$). There were no significant differences between any other regions. Over 90% of the therapists stated that TJM were most often performed in the thoracic spine and least frequently in the upper cervical spine (less than 50%) (FIGURE 1).

Figure 1. Levels of agreement with the statement "I regularly provide Thrust Joint Manipulation to the XXX spine where it is indicated."

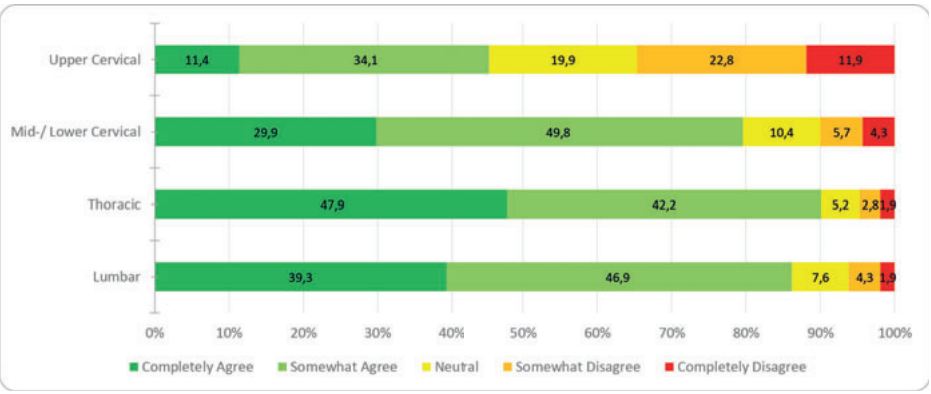


Friedman's revealed significant differences between upper cervical and lumbar (p = 0.000), upper cervical and thoracic (p = 0.000), upper cervical and mid/ low cervical (p = 0.000), mid/ low cervical and thoracic (p = 0.000).

SAFETY AND EFFECTIVENESS OF TJM BY SPINAL REGION.

A significant difference in perceived safety and effectiveness was found across spinal region (x^2 (3) = 249.371, p < 0.000). Post hoc tests illustrated differences between upper cervical and mid/ low cervical (p = 0.000), upper cervical and thoracic (p = 0.000), upper cervical and lumbar (p = 0.000), mid/ low cervical and thoracic (p = 0.003). There were no significant differences between any other regions. Respondents believed that TJM was most effective and safe in the thoracic spine, followed by the lumbar and the mid/ low cervical spine. The upper cervical spine was deemed least effective and safe for TJM (FIGURE 2).

Figure 2. Levels of agreement with the statement "Thrust Joint Manipulation in the XXX spine is safe and effective for patients in which it is indicated."

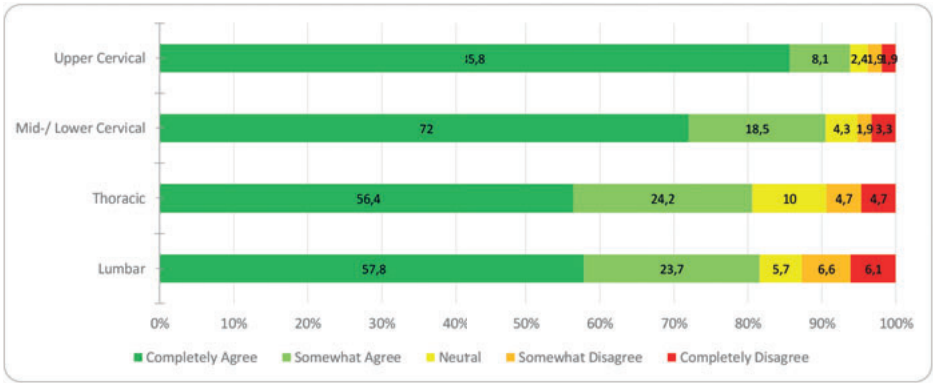


Friedman's revealed significant differences between upper cervical and mid/ low cervical (p = 0.000), upper cervical and thoracic (p = 0.000), upper cervical and lumbar (p = 0.000), mid/ low cervical and thoracic (p = 0.003).

Additional screening prior to TJM by spinal region

A significant difference was found between the regions. x^2 (3) = 144.578, p < 0.000. Post hoc tests demonstrated significant differences between upper cervical and lumbar (p = 0.000), upper cervical and thoracic (p = 0.000), mid/ low cervical and lumbar (p = 0.005), mid/ low cervical and thoracic (p = 0.003). There were no significant differences between any other regions. Respondents reported to screen the upper cervical spine more than the other regions. Still, 90.5% of the respondents would routinely perform additional screening to the mid/lower cervical spine. For the thoracic and lumbar spine this was less with 81% and 82%, respectively (FIGURE 3).

Figure 3. Levels of agreement with the statement "Prior to performing Thrust Joint Manipulation to the XXX spine, I would routinely perform additional screening."

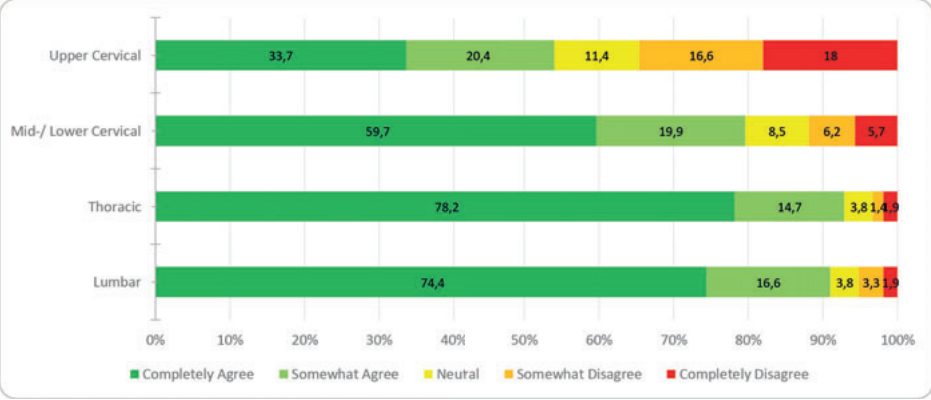


Friedman's revealed significant differences between upper cervical and lumbar (p = 0.000), upper cervical and thoracic (p = 0.000), mid/ low cervical and lumbar (p = 0.005), mid/ low cervical and thoracic (p = 0.003).

Comfort performing TJM by spinal region

A significant difference was found between the regions. x^2 (3) = 270.514, p < 0.000. Post hoc tests showed significant differences between upper cervical and lumbar (p = 0.000), upper cervical and thoracic (p = 0.000), upper cervical and mid/ low cervical (p = 0.000), mid/ low cervical and thoracic (p = 0.009). There were no significant differences between any other regions. Therapists agreed they were most comfortable performing TJM in the thoracic spine. Applying TJM to the upper cervical spine made therapists least comfortable (FIGURE 4).

Figure 4. Levels of agreement with the statement "I am comfortable performing Thrust Joint Manipulation to the XXX spine in patients that require it."



Friedman's revealed significant differences between upper cervical and lumbar (p = 0.000), upper cervical and thoracic (p = 0.000), upper cervical and mid/ low cervical (p = 0.000), mid/ low cervical and thoracic (p = 0.009).

INFLUENCE OF CLINICAL EXPERIENCE

MANOVA showed no differences in the years of clinical experience in manual therapy for all four statements. Working experience did not seem to influence the respondent's answers.

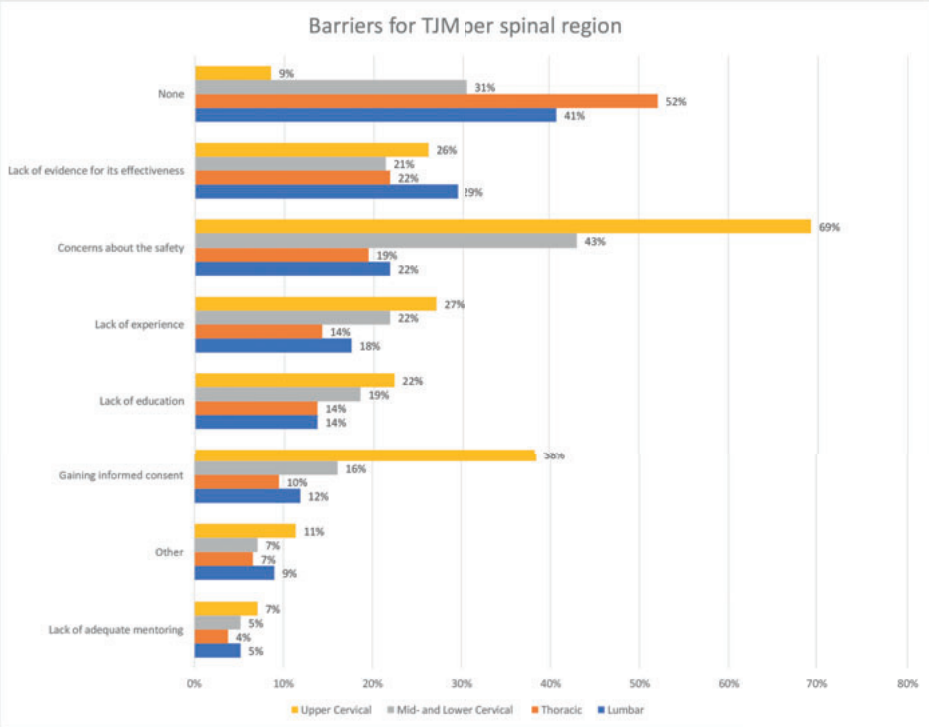
Statement: "I regularly provide Thrust Joint Manipulation to the XXX spine where it is indicated." Wilks' Lambda = .952, F=1.269, p=.258

Statement: "Thrust Joint Manipulation in the XXX spine is safe and effective for patients in which it is indicated." Wilks' Lambda = .967, F=0.852, p=.558

Statement: "Prior to performing Trust Joint Manipulation to the XXX spine, I would routinely perform additional screening." Wilks' Lambda = .984, F=0.419, p=.909

Statement: "I am comfortable performing Thrust Joint Manipulation to the XXX spine in patients that require it." Wilks' Lambda = .960, F=1.040, p=.405

Figure 5. Barriers to the use of TJM by Dutch manual physical therapists



Percentage of respondents choices for provided options as well as 'Other' which then allowed for text entry.

The results that stand out most are the lack of barriers to perform thoracic TJM, the concerns about the safety of TJM for the upper cervical region and gaining informed consent for the upper cervical region. For the lumbar region: high pain score, pain in end range, arthrosis, pregnancy, hypermobile, pathology, age, co-morbidity, muscle control impairment, contraindications, medication, radicular syndrome and red flags were mentioned as 'others'. For the thoracic spine: pregnancy, arthrosis, cancer, elderly, comorbidity, pathology, contraindications, medication, osteoporosis and internal organ projection. For the mid and lower cervical spine: Pregnancy, cancer, arthrosis, osteoporosis, pathology, elderly, comorbidity, contraindications, medication and red flags. Cancer, pregnancy, arterial disease, contraindications, medication and red flags were mentioned for the upper cervical spine.

DISCUSSION

To our knowledge, this is the first study that has described the utilization of spinal TJM, perceptions of TJM safety and effectiveness, and perceived barriers to utilization of spinal TJM for Dutch manual therapists. Findings suggest that Dutch manual therapists generally believe TJM is a safe and effective treatment approach except for the upper cervical spine. They frequently apply TJM in the management of their patients. Dutch manual therapists feel comfortable performing TJM in the thoracic, lumbar, and to a lesser extent, in the lower-/ and mid cervical spine. Half of the respondents have doubts concerning the safety and effectiveness of TJM applied in the upper cervical spine. Therefore, utilization and comfort in performing upper cervical TJM differs considerably from other regions with several reported barriers being identified.

UTILIZATION AND BELIEFS ABOUT SAFETY OF TJM

The results of this study show that in the Netherlands, the cervical spine is the most often treated spinal region by manual therapists (36%). Respondents were most reserved to use TJM, were less confident, less comfortable and worried most about the safety of the TJM techniques in the cervical, compared with other regions. Differences between the upper cervical spine and the mid-/ lower cervical spine were notable with most respondents (69%) reporting concerns about safety as a barrier for the use of TJM in the upper cervical region, compared to just 43% in the mid-/ lower cervical spine. While 45.5% of the respondents completely agreed or somewhat agreed that TJM in the upper cervical spine were safe and effective, 90% of the respondents had the opinion that TJM in the mid-/ lower cervical spine were safe and effective.

CERVICAL SPINE

Only 45.5% of the respondents ‘somewhat agreed’ or ‘completely agreed’ that TJM in the upper cervical spine is a safe treatment technique, whilst 54.1% of the respondents are comfortable performing TJM in the upper cervical spine; perhaps attributable to inconclusive evidence of risk and benefit of the technique. (Kranenburg et al., 2017) It could also be that manual therapists find it difficult to acquire written informed consent when no other physical therapeutic intervention requires such consent in the Netherlands; 40% of the respondents perceived the written informed consent sheet as a barrier to performing upper cervical spine TJM. Our findings mirror a recent review of Australian manual therapists where reported negative perceptions like time constraints, evidence update necessary and raising unnecessary risk awareness as possible factors limiting the use of

manual therapy.(Thomas et al., 2019) Although informed consent comprises ethical and legal components, there are different types of consent.(Rushton et al., 2014) Fundamentally, consent is integral to clinical reasoning and should be an ongoing process.(Rushton et al., 2014) The scope and nature of informed consent provided by each therapist in currently unknown.

THORACIC SPINE AND LUMBAR SPINE

More than half (52%) of the respondents experience no barriers for TJM in the thoracic region, and over 90% are comfortable performing TJM in that region. Although respondents are confident and often perform TJM in the thoracic region, 80.6% of the respondents would routinely perform additional screening prior to thoracic TJM, differing considerably to the reported data from the UK where this this is just 39.7% of respondents.(Heneghan et al., 2018) The content of the pre TJM examination is unknown. Whilst a detailed patient history underpins advanced clinical reasoning and selecting treatment interventions, advice for pre-manipulative testing remains unclear in the thoracic spine.(Heneghan et al., 2018; Puentedura and O'Grady, 2015) Similar results are seen in the lumbar spine, a considerable number of respondents are applying 'additional screening' of unknown content prior to lumbar TJM.

In the U.S., only 33% of the physical therapists reported they regularly provided TJM to the cervical spine.(Puentedura et al., 2017) A difference in utilization of TJM was also found in the UK, where the use of TJM for C0/C1, C1/C2, and C2/3-C4-C5 significantly differed, compared to C5/C6-C7/T1, and thoracic and lumbar spine. In that study, the reported use of TJM at C0/C1 (24%) and C1/C2 (22%) was only half the reported use of TJM at C2/C3 (66%), and only one third of the use of TJM at C5/C5-C7-T1 (80%).(Adams and Sim, 1998) The results from our survey differ from the results of the study conducted in the U.S. For the lumbar spine, in the U.S. 52.9% regularly provide TJM (Puentedura et al., 2017), while in the Netherlands this percentage is 86.2%. In the Netherlands, TJM for the thoracic spine is more frequently used (93.3%) than in the U.S (66.5%).(Puentedura et al., 2017) This difference may be due to the fact that we surveyed only manual physical therapists whereas in the U.S. study, Puentedura et al. (Puentedura et al., 2017) surveyed all licensed physical therapists regardless of their practice setting. In the U.K., Adams and Sim found rates for the lower cervical region of 80% -, 66% for the middle cervical,- 22-24% for the upper cervical-, 97% for the lumbar-, and 92% for the thoracic spine. (Adams and Sim, 1998)

ADVANCED TRAINING

Respondents of our survey were Dutch manual therapists, who had completed a 3-year post-entry-level master's degree in PT. Whereas in the U.S. study, all physical therapists were surveyed. Advanced training can influence the reasoning, decision making and skills of therapists. Nonetheless, advanced training also comprises critical reasoning and knowledge of the IFOMPT educational standards about possible risks that may occur.(Rushton et al., 2014)

STRENGTHS AND LIMITATIONS

A strength of this study is that it was based on a comparable survey.(Puentedura et al., 2017) Because we also surveyed barriers for each separate spinal region, this study provides an insight into the barriers for each spinal region as well. Results were analyzed for differences influenced by years of respondents' clinical experience.

This study has some limitations. Completion of the survey did not require a login so individuals could respond using multiple devices. Findings are subject to selection bias, with launch being at the annual National manual therapy conference (approximately 500 participants), posted on the website of the Dutch Association for Manual Therapy (approximately 2000 members), distributed via social media (Twitter, Facebook and LinkedIn) and word of mouth by the researchers in their network. In addition, the respondents of which 211 fully completed surveys, represented approximately 5% of the registered Dutch manual therapists, limiting the generalizability of findings

IMPLICATIONS FOR CLINICAL PRACTICE

Notwithstanding the limitations, study findings emphasize the importance of contemporary clinical practice of Dutch manual therapy being founded on current evidence of the risks and benefits of upper cervical spine versus low/ middle cervical spine TJM. Theoretically, it is possible that Dutch manual therapists might be overcautious regarding performance of TJM in the upper cervical spine. If the associated risk or contributing factor to cervical artery dysfunction is the manipulative position, then arguably this then also applies to mid/ lower cervical spine and upper thoracic spine TJM and not just for the upper cervical spine. Currently there appears insufficient evidence to support differentiating practice across some spinal regions. Whilst the occurrence of adverse events following TJM is rare, practitioners should however remain alert to the risks of TJM in the lower cervical and thoracic spine.

FUTURE RESEARCH

Qualitative or mixed methods research could be helpful to explore the process and nature of consent in manual therapy, investigate the experiences with gaining pre-manipulative informed consent, and to identify whether barriers might lead to the use of TJM without such written informed consent. Furthermore, it might be of value to explore the various options for obtaining a more standardized informed consent.

CONCLUSION

Findings suggest Dutch manual therapists are comfortable and confident in using TJM in the spine. Excluding the upper cervical spine, respondents feel that TJM's are safe to use. Consequently, most barriers for the use of TJM were reported for the upper cervical spine and comprised concerns about safety.

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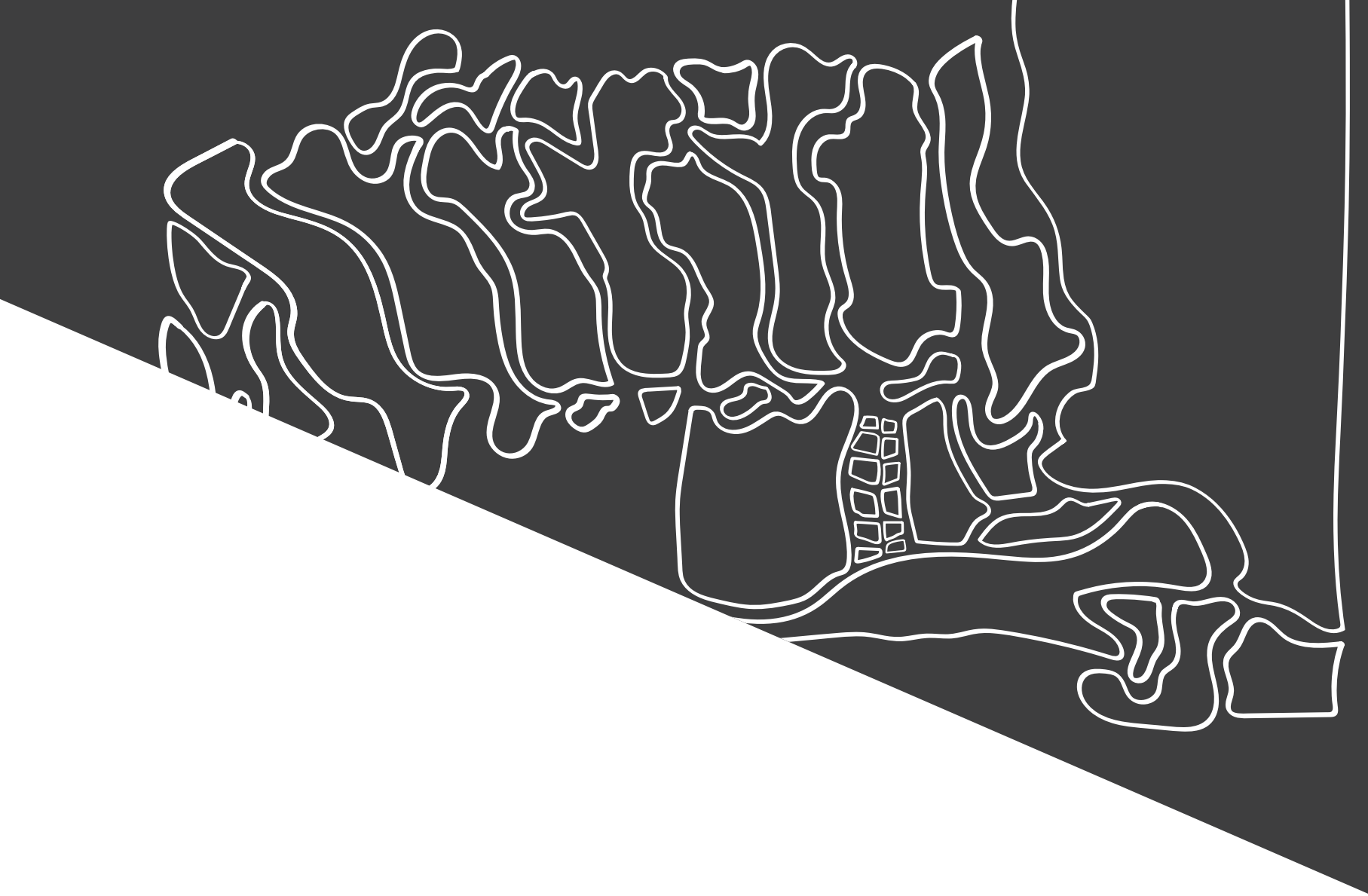

ADVERSE EVENTS FOLLOWING CERVICAL MANIPULATIVE THERAPY: CONSENSUS ON CLASSIFICATION AMONG DUTCH MEDICAL SPECIALISTS, MANUAL THERAPISTS, AND PATIENTS

3

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ABSTRACT

Objectives: To obtain consensus-based agreement on a classification system of adverse events (AE) following Cervical Spinal Manipulation. The classification system should be comprised of clear definitions, include patients' and clinicians' perspectives, and have an acceptable number of categories.

Method: Design: A three round Delphi-study.
Participants: Thirty Dutch participants (medical specialists, manual therapists, and patients) participated in an online survey.
Procedure: Participants inventoried AE and were asked about their preferences for either a three or a four-category classification system. The identified AE were classified by two analysts following the International Classification of Functioning, Disability and Health (ICF) and the International Classification of Diseases and Related Health Problems (ICD-10). Participants were asked to classify the severity for all AE in relation to the time duration.

Results: Consensus occurred in a three-category classification system. There was strong consensus for 16 AE in all severities (no, minor, and major AE) and all three-time durations [hours, days, weeks]. The 16 AE included anxiety, flushing, skin rash, fainting, dizziness, coma, altered sensation, muscle tenderness, pain, increased pain during movement, radiating pain, dislocation, fracture, transient ischemic attack, stroke, and death. Mild to strong consensus was reached for 13 AE.

Discussion: A consensus-based classification system of AE is established which includes patients' and clinicians' perspectives and has three categories. The classification comprises a precise description of potential AE in accordance with internationally accepted classifications. After international validation, clinicians and researchers may use this AE-classification system to report AE in clinical practice and research.
Level of Evidence: 5

INTRODUCTION

Adverse events (AE) may occur as a consequence of Cervical Spinal Manipulations (CSM). Adverse events are unexpected events that occur following an intervention without evidence of causality.(Carlesso et al., 2010b) Major adverse events such as Cervical Arterial Dissection (CAD), Cerebral Vascular Accident, or death only rarely occur.(Carlesso et al., 2010a; Cassidy et al., 2008) Incidence rates of major adverse events were estimated between 1 to three thousand and 1 to six million.(Assendelft et al., 1996; Magarey et al., 2004; Nielsen et al., 2017) In general, it is likely that the incidence rates of AE are underreported.(Ernst, 2007; Kranenburg et al., 2017; Shekelle, 2007; Wynd et al., 2013) This could possibly be due to the lack of standard definitions of AE and the absence of a clear, uniform classification system that combines the severity and duration of the AE.(Carlesso et al., 2010b; Carnes et al., 2010; Thomas, 2016; Wynd et al., 2013) A note of caution is due in this context since not all AE occur at the time of the intervention. It could happen that the therapist is not aware of an AE when not alerted by the patient. Additionally, a clinician might not always be willing to be open about the presence of an AE. Gorrell et al. (Gorrell et al., 2016) emphasized the importance of a uniform standardized nomenclature classification system and development and validation of AE reporting tools to collect and pool data in the future.

A clear classification system begins with clarifying the construct of an AE. Multiple terms are used to describe the harm caused following cervical mobilization or manipulation. Most have their origin in the pharmacovigilance field but are not completely appropriate for orthopedic physical therapy. Most of the existing terms imply causality with the used technique. Causalities of AE following CSM have been suggested, but are not confirmed.(Carlesso et al., 2010b) A clear classification system with standard definitions, that combines severity and time duration of adverse events is advantageous for implementation as an incident reporting system by professional or national independent associations. Such an unambiguous AE system may facilitate manual therapists in reporting AE.(Carlesso et al., 2010b; Carnes et al., 2010; Dionne et al., 2008; Puentedura et al., 2012) In research, the classification system described by Carnes et al. (Carnes et al., 2010) is regularly used.(Carlesso et al., 2011; Paanalahti et al., 2014) While defining potential AE in that study by means of a Delphi method, consensus was established for only 15 of 36 presented potential AE.(Carnes et al., 2010) There is a myriad of possible reasons why the participants of the latter study did not achieve consensus on a more extensive number of potential AE. For example, first, the response rate of the participants was minimal (Round 1--50%, Round 2--62%, and Round 3--55%). Low response rates may be vulnerable for

selection bias and outlier opinions may be difficult to neutralize. Secondly, the AE were divided into four categories: no, minor, moderate, and major AE. This division may be too complex to use as there is more debate about what is a minor or a moderate AE than what is not an AE or what is a major AE.(Carlesso et al., 2011) Thirdly, definitions of a potential AE may not have been clearly described. A set of more precisely described definitions might enhance clarity between participants. In both research and clinical practice, there is a need for a clear consensus-based classification system of AE following CSM.(Schulz et al., 2010) The aim of this study, therefore, was to develop a system which meets the following criteria: 1] beneficial for research and clinical practice, 2] includes patients' and clinicians' perspectives, 3] has an acceptable number of categories and clear definitions, and 4] is based on an accepted international classification of diseases (ICD-10) and international classification of functioning, disability and health (ICF).

METHOD

DESIGN

A three-round modified digital Delphi study was performed from September 2013 to January 2014 (Figure 1).(Keeney et al., 2011; McKenna, 1994) The Delphi technique is a structured approach that is employed to achieve consensus anonymously among a panel of experts and is a well-established technique for consensus building among participants.(Avery et al., 2005; Keeney et al., 2006; Thompson, 2009) Following each round, the panel members can anonymously observe the group opinions, compare the group opinions with their own responses, and may even reconsider them. The online survey program SurveyMonkey was used to inventory the panel members' opinions.(SurveyMonkey, n.d.)

PARTICIPANTS, THERAPISTS, CENTERS

To achieve a broad perspective of input, a heterogeneous sample of Dutch participants (panel members) was recruited. They were selected from three relevant expert groups: 1] medical specialists; 2] manual physical therapists (MT's); and 3] patients. A total of 30 panel members were included with a quota of ten members per expert group. Medical specialists (i.e., neurologists or orthopedic surgeons) were recruited from four hospitals, patients were recruited from three different private clinics, and the MTs were randomly invited. The first author asked contact persons (medical specialists and manual therapists) through emails to outpatient clinics and hospitals nationwide to invite potential participants in their own institution. The contact persons provided a list of potential participating panel members who were asked through emails to participate. Potential panel members were also

asked to recruit other potential panel members (snowball-sampling method). This recruitment process was executed for both medical professionals and patients. By selecting hospitals and clinics nationally, there was an attempt to create a varied spread of participants during the invitation process.

Prior to the selection of panel members, inclusion criteria were established: 1] medical specialists working with or who could receive patients that experienced AE after CSM. No more than two panel members with the same specialization were allowed; 2] manual therapists; i.e., physical therapists who had graduated from programs accredited by the country's national Orthopedic Manual Therapy organization.; 3] patients over 18 years old who suffered from neck pain and had been treated by a manual therapist and experienced a CSM at least once; and 4] all panel members had to be native Dutch speakers. The panel was limited the Dutch nationality as an international panel would imply multiple translations and interpretations which would reduce the reliability of the results of this study.

DELPHI PROCESS

All panel members signed informed consent and received an individualized unique participation code. In an attempt to ensure quasi-anonymity, only the first author (RK) was aware of this code.(Keeney et al., 2011) This Delphi study was comprised of three rounds. During each round, the survey was available for 21 days. Those members who did not initially respond received a personal reminder by email from the first author after ten, 17, and 20 days. Each panel member could miss one round before being excluded from further participation. All were invited during each round to make further comments on each of the questions.

The following decision criteria were specified a-priori; 1] strong consensus was predetermined at ≥ 75%; 2] in Round 1, participants were asked to select either a system with three or four categories to classify. The number of categories as a result of Round 1 was used in Round 2; 3] if no consensus was reached for ten AE over four categories in Round 2, the three categorical system was employed in Round 3. An independent Medical Ethical Committee of the University Medical Center Groningen, The Netherlands approved a waiver for this research protocol. This waiver stated that the "Medical Research Involving Humans Act" (WMO) did not apply for this study.

INTERVENTION

ROUND ONE

The aim of Round 1 was twofold; 1] to inventory all possible adverse events following CSM, and 2] to reach consensus on either a three or four categorical AE classification system (Figure 1). (Keeney et al., 2011)

1. Identification of adverse events

As Carnes et al. (Carnes et al., 2010) described the most comprehensive list of AE, this list was designated as a base and was provided to the panel members. To translate the AE of Carnes et al.'s (Carnes et al., 2010) list into Dutch, a forward-backward translation strategy was employed by the first author and a native bilingual manual therapist.(Maneesriwongul and Dixon, 2004) During Round 1, panel members were asked to indicate potential AE from Carnes et al.'s list.(Carnes et al., 2010) Panel members were also asked to add items to the list that they considered as possible AE.

2. Categories

Panel members were directed to select one of the two categorical classification systems. The first option was a system of four categories as proposed by Carnes et al. (Carnes et al., 2010): not adverse, minor, moderate, or major AE. The second option was a categorical classification system of three categories instead of four: not adverse, minor adverse, or major AE.

ROUND TWO

Time and severity

Round 2 aimed at obtaining agreement on the influence of the length of time that the AE lasted against the severity of the AE. For the length of time, the time units as described by Carnes et al. (Carnes et al., 2010) (hours, days, and weeks) were used. For severity, the AE were analyzed in accordance with the Carnes et al.'s (Carnes et al., 2010) four categorical classification. If a unanimous preference was reached in Round 1 for our proposed three categorical classification, then the AE were analyzed in the three categorical classification. Using a selection table, the panel members were asked to indicate the severity of an adverse event in relation to the time in which it had occurred.

ROUND THREE

The aim of Round 3 was to validate the answers of Round 2. When proceeded in the four categorical system; for each potential AE, the panel members own opinion

and the group opinion was presented. If a panel member agreed with the opinion provided by the majority of panel members, the next item was presented. If they did not agree with the opinion provided by the majority, they were asked to re-indicate their opinion. If 100% consensus from all the responding panel members in Round 2 was already reached, no question was needed, and the results were shown to all panel members.

However, following the third a-priori specified criteria; if no consensus was reached for ten AE over four categories in Round 2, then the number of categories was adjusted in preparation for Round 3. Panel members' indication of AE as chosen in the four categorical classification system was validated within the three categorical classification system. Validation was performed by asking each panel member again if their indication of Round 2 resembles the third round. This was established by showing each panel member their individual opinion of the second round and the groups' panel opinions of Round 2. If a panel member agreed with the answer provided by the majority of panel members, the next item was presented. If they did not agree with the answer provided by the majority, they were asked to restate their opinion. Also, if 100% consensus from all the responding panel members in Round 2 was already reached, the results were shown to all panel members.

DATA ANALYSES

DATA ANALYSES ROUND ONE

Definitions of adverse events

If one of the panel members indicated that an item in Round 1 was a possible AE, the item proceeded to Round 2. The first author (RK) and the second author (SL) individually linked all the AE from Carnes et al. 's (Carnes et al., 2010) list and the AE that the panel members had added to the ICF or the ICD-10.(World Health Organisation, 2012, 2001) The ICF and ICD-10 provide a systematic coding and clear definitions. In the event of a dispute or uncertainty, the opinion and advice was sought from the last author (CS).

Categories

Panel members were subsequently asked to select one of the two categorical classification systems. Since the four categorical classification proposed by Carnes et al. (Carnes et al., 2010) has been used in published research, the potential AE in Round 2 were presented accordingly. However, if in Round 1 the panel members reached a strong consensus for our proposed three categorical classification system, then the potential AE were presented in that manner.

DATA ANALYSES ROUND TWO

A modification of a linked ICF or ICD-10 definition could occur if one of the participating panel members advised to do so during Round 1. However, it could only be changed if both authors (RK, SL) agreed to the change. In the event of a dispute or uncertainty, the opinion of the last author (CS) was sought. In preparation for the third round, the modes of the groups' AE (exhibited in percentages) were calculated.

If the panel members reached consensus on less than ten AE in Round 2 by using the four categories, AE's were analyzed into the three categories based on the assumption that additional consensus was reached using three categories instead of four. To convert the answers from the classification in four categories to the classification in three categories, the answers of moderate AE were merged with the answers of minor AE and labeled as minor AE. The underlying motivation for this merger was the assumption that these categories overlap the most and, therefore, incite the most debate.(Carlesso et al., 2011)

DATA ANALYSES ROUND THREE

Degree of consensus

A pre-determined level of consensus was employed, which is often referred to as the Majority Rule.(Hasson et al., 2000) The most common percentage for agreement is 75%.(Diamond et al., 2014) Setting direction to consensus was first described in 1995 and later further refined by O'Loughlin and Meskell.(de Loe, 1995; Meskell et al., 2013; O'Loughlin and Kelly, 2004) For this study, mild consensus was established at 60% to 74% agreement (Table 1). Strong consensus was specified whereby at least 75% of the panel members agreed on an AE.(Awad and Alghadir, 2013; Carnes et al., 2010; Glocker et al., 2013)

Table 1. Level of Consensus

Level of Agreement	***Level of Consensus***
0% - <60%	No consensus
60% - <75%	Mild consensus
75% - 100%	Strong consensus

RESULTS

FLOW OF PARTICIPANTS, THERAPISTS, CENTERS THROUGH THE STUDY

A total of 30 experts responded positively to the invitation and signed the informed consent (Table 2). The medical specialist group consisted of two neurologists, one neurosurgeon, one orthopedist, one orthopedic surgeon, one trauma surgeon, one emergency physician, one sports physician, and two general practitioners. All group members in the manual therapy group had obtained a master's degree and were practicing manual therapy in a private setting. Three of them were also teachers at a university of Master Manual Therapy education and three others at a university of Bachelor Physical Therapy education. An eleventh manual therapist was added based on his broader perspective due to his work as a full-time Professor of Rehabilitation Medicine. One of the patient panel members withdrew for unknown reasons after the first round. No panel member was excluded for Round 3. Furthermore, panel members were geographically dispersed nationwide.

Table 2. Three Round Response Rate for Panel Members

Round	*Total response*	*Medical Specialists*	*Manual Therapists*	*Patients*
1	27 (90%)	8 (30%)	11 (41%)	8 (30%)
2	27 (90%)	10 (37%)	11 (41%)	6 (22%)
3	23 (77%)	8 (35%)	10 (43%)	5 (22%)

ROUND 1

Definitions of adverse events

All 37 items listed by Carnes et al. (Carnes et al., 2010) were identified by at least one panel member as a potential AE after CSM. The panel members returned 12 new suggestions for potential AE. Six panel members indicated that they required more specific definitions for some of the suggested potential AE. During the analysis and following the linking of AE to ICF and ICD-10 definitions, some of the items were combined if they had the same ICF or ICD-10 code such as vomiting and puking. The final list comprised 34 items related to ICF or ICD-10 definitions (Appendix 1).

Categories

Of the panel members, 55.6% preferred the four categorical classification proposed by Carnes et al. (Carnes et al., 2010), and 44.4% favored the three categorical classification of events. Therefore, no unanimous preference on the categories of classification was achieved. Following the method section, we preceded the Delphi-

study with the four category classification as proposed by Carnes et al. (Carnes et al., 2010)

ROUND 2

Time and severity

All responding panel members determined that death and stroke were major AE. During the analysis procedure of division into four categories, strong consensus was reached for eight potential AE, and no (strong) consensus was reached for 16 potential AE. Therefore, the study was subsequently continued with the three categorical classification system. Consequently, the answers of minor and moderate AE were merged into minor AE and returned as three categorical answers to the panel members.

Definitions of adverse events

To the definition of AE 'Skin Rash', the following was amended: it concerns a local area at the manipulated segment. The definition of AE 'Fainting' was further specified by addition that it concerns repeated fainting in the specified time. Loss of consciousness generally occurs within one-two minutes. Dizziness was divided into two different AE, namely, ICD-10 H81.9 disorder of vestibular function, unspecified, and ICD-10 R42 dizziness and giddiness. For the AE "migraine", the option of "weeks" was removed because migraine has a maximum duration of three days.(Headache Classification Subcommittee of the International Headache Society, 2004) Two members of the medical panel asked specific questions regarding the AE 'loss of or reduced bladder control' and 'loss or reduced bowel control', as it was important for them to know whether it concerned incontinence or constipation. After consulting with an independent medical specialist for an expert opinion regarding a specification of the definition, it was added that both adverse events primarily concerned incontinence.

ROUND 3

Consensus

After showing the panel members their individual indications of AE in the three categorical classification system and the indications of the majority of panel members, consensus was reached for 29 of the 34 AE for all durations (hours, days, weeks) (Table 3). Regarding the remaining five AE (Depression, Joint pain, Vertigo, Visual disturbance and Panic attack) consensus was obtained for two of the three durations [hours, days, weeks].

Degree of Consensus

For 16 of the 34 AE, a strong consensus (at least 75% of the panel members agreed on an AE) was reached for all durations [hours, days, weeks] (Table 3.1). These AE were: anxiety, altered sensation, coma, death, dislocation, dizziness, fainting, flushing, fracture, increased pain during movement, muscle tenderness, pain, radiating pain, skin rash, stroke and transient ischemic attack. The remaining 13 AE in which consensus was gained, were combined mild-strong consensus results (Table 3.2). Mild consensus (60% to 74% agreement) was only reached in the category Minor AE. Furthermore, six panel members (four physicians and two manual therapists) noted for 14 adverse events that they could not determine the relationship between a CSM and the potential AE. No panel member from the patient panel noted comments to the responses.

Table 3. Consensus Results; severities and time durations.
3.1 Full Consensus (Strong) for all severities and all time durations.

		No Adverse Event	***Minor Adverse Event***	***Major Adverse Event***
Anxiety ICF-B152	*Hours*		*Strong consensus*	
	Days		*Strong consensus*	
	Weeks		*Strong consensus*	
Altered sensation ICF-B279	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks			Strong consensus
Coma ICF-B110	Hours			Strong consensus
	Days			Strong consensus
	Weeks			Strong consensus
Death				Strong consensus
Dislocation ICF-B7150				Strong consensus
Dizziness ICD10-R42	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks			Strong consensus
Fainting ICD10-R55	Hours		Strong consensus	
	Days			Strong consensus
	Weeks			Strong consensus

3.1 Continued

		No Adverse Event	*Minor Adverse Event*	*Major Adverse Event*
Flushing ICD10-R23.2	Hours	Strong consensus		
	Days		Strong consensus	
	Weeks		Strong consensus	
Fracture ICD10-S12				Strong consensus
Increased pain during movement ICF-B2801	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks			Strong consensus
Muscle tenderness ICD10-M79.1	Hours	Strong consensus		
	Days		Strong consensus	
	Weeks		Strong consensus	
Pain ICF-B2801	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks			Strong consensus
Radiating pain ICF-B2803	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks			Strong consensus
Skin rash ICD10-L98	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks		Strong consensus	
Stroke ICD10-I69				Strong consensus
TIA ICD10-G45				Strong consensus

3.2 Full Consensus (Mild or Strong) for all severities and all time durations

		No Adverse Event	***Minor Adverse Event***	***Major Adverse Event***
Breathing difficulties ICF-B440	Hours		Mild consensus	
	Days			Strong consensus
	Weeks			Strong consensus
Control of voluntary movements ICF-B760	Hours		Strong consensus	
	Days		Mild consensus	
	Weeks			Strong consensus
Deafness ICD10-H91.9	Hours		Mild consensus	
	Days			Strong consensus
	Weeks			Strong consensus
Fatigue / Yawn CD10-R53	Hours	Strong consensus		
	Days		Mild consensus	
	Weeks		Strong consensus	
Headache ICF-28010	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks		Mild consensus	
Loss of movement ICF-B710	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks		Mild consensus	
Loss or reduced bladder control ICF-B6200	Hours		Mild consensus	
	Days			Strong consensus
	Weeks			Strong consensus
Loss or reduced bowel control ICF-B5253	Hours		Mild consensus	
	Days			Strong consensus
	Weeks			Strong consensus
Migraine ICD10-G43	Hours		Strong consensus	
	Days		Mild consensus	
Nausea ICF-5350	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks		Mild consensus	
Palpitations ICD10-F45.3	Hours		Strong consensus	
	Days		Mild consensus	
	Weeks			Strong consensus

3.2 Continued

		No Adverse Event	*Minor Adverse Event*	*Major Adverse Event*
Severe sweating ICD10-F45.3	Hours		Mild consensus	
	Days		Strong consensus	
	Weeks		Mild consensus	
Vomiting ICD10-R11	Hours		Strong consensus	
	Days		Mild consensus	
	Weeks			Strong consensus

3.3 Partial consensus for all severities and all time durations

		No Adverse Event	*Minor Adverse Event*	*Major Adverse Event*
Depression ICD10-F32	Hours		Mild consensus	
	Days	No consensus	No consensus	No consensus
	Weeks		Mild consensus	
Joint pain ICD-M25.5	Hours		Strong consensus	
	Days		Strong consensus	
	Weeks	No consensus	No consensus	No consensus
Panic attack ICD10-F41	Hours		Mild consensus	
	Days	No consensus	No consensus	No consensus
	Weeks			Strong consensus
Vertigo ICD10-H81.9	Hours		Strong consensus	
	Days	No consensus	No consensus	No consensus
	Weeks			Strong consensus
Visual disturbance ICF-B210	Hours	No consensus	No consensus	No consensus
	Days		Mild consensus	
	Weeks			Strong consensus

DISCUSSION

A consensus-based classification system of AE following CSM was established. It includes patients' and clinicians' perspectives, it comprises an acceptable number of categories (no, minor, and major AE), it incorporates a precise description of potential AE, and it is based on internationally accepted classifications (ICD-10 and ICF). Mild to strong consensus was achieved on 29 of the 34 AE for all durations [hours, days, weeks]. For the remaining five AE, consensus was reached for two of the three durations [hours, days, weeks].

For use in daily practice, it is essential for clinicians that AE can be rapidly classified and without too much difficulty, i.e., the fewer the choices, the better the consensus. In our study, a three categorical classification system was developed in which the word 'moderate' was not included, and patients' opinions were included in the Delphi process. Patient opinions were included, because they are considered an important part of shared decision making. Therewith, we added a new perspective to the previous Delphi process as described by Carnes et al.(Carnes et al., 2010) Furthermore, in our classification we integrated all durations for all AE when applicable and reached consensus on 29 AE for all the durations. Because symptoms of AE such as vomiting and puking can be considered as one and the same, we used ICF/ ICD-10-linking rules. Aligning nomenclature for symptoms creates a better understanding of the variety between symptoms and may also simplify the reporting of AE. To the authors' knowledge, this is the first study in which AE were linked to other classification systems (ICF and ICD-10) whereby a wide-ranging expert panel participated. Also, the introduction of two levels of consensus (mild and strong consensus) is new and supports transparency in the quality of consensus.

The results in this study are strengthened the consistent high overall response rate during all three rounds. i.e., 90% for the first two rounds and 77% for the third round, which indicates substantial validity of the results.
Even though this study was not internationally performed, and the ICF and ICD-10 were followed, the results may not be generalizable to other world regions but the suggested definitions could be used for international research towards validating the results within clinicians and researchers of other countries. Additionally, before this classification system can be considered internationally useful, it should produce valid interpretations of datasets in several languages.
Although all described AE were identified by the panel as possible AE following CSM, the causality of AE after CSM is complex and not supported by all criteria of causation.(Haynes et al., 2012; Tuchin, 2014) Despite the importance, the causality of AE is not addressed in this study.

There are several limitations in this study that should be critically appraised. Although potential AE were accumulated over a period of time, the severity of AE themselves remains undefined. For example, pain could be described more accurately by using the Numeric Rating Scale (NRS). The next point of consideration is that this study approached all potential AE as isolated AE even though the simultaneous occurrence of more than one minor AE might be considered as a major AE from a patient's or a therapist's perspective.(Carnes et al., 2010) Sampling

bias may have occurred; the sample of manual therapists may have been prejudiced since more than half of the (n=6) panel members were also teaching to physical and manual therapy students. Finally, statistics were not applied to the detailed results. (Appendix 2). However, contrary to what other studies indicate, it seems no differences in opinions were ascertained between the patient panel versus the medical and manual therapy panels (Appendix 2).(Rajendran et al., 2012; Weissman et al., 2008)

In order to improve the feasibility of the list in daily practice or research, it is proposed that: 1] the quality of the list of AE should be internationally tested for validity; 2] clinicians add new AE to the current list and assess the time of this newly defined AE by the severity, as was done in this study; 3] a distinction between causes (i.e., fracture or arterial dissection) and signs/symptoms (i.e., pain and vomiting) be performed.

Additionally, it might be advisable to assist manual therapists in classifying and/or reporting AE with additional education. It is also recommended to obtain agreement on specific AE that should then be reported to a central organization. If, after international validation, our classification is used as a base for an incident reporting system, it could fill a gap between science and everyday practice.

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APPENDICES

APPENDIX 1

Appendix 1. Adverse Events: linked ICF/ ICD10 codes and definitions.

Adverse Event	***Code***	***Definition***
Altered sensation	ICF-B279	Additional sensory functions, other specified and unspecified
Anxiety	ICF-B152	Specific mental functions related to the feeling and affective components of the processes of the mind. Incl.: functions of appropriateness of emotion, regulation and range of emotion; affect; sadness, happiness, love, fear, anger, hate, tension, anxiety, joy, sorrow; lability of emotion; flattening of affect
Breathing difficulties	ICF-B440	Functions of inhaling air into the lungs, the exchange of gases between air and blood, and exhaling air. Incl.: functions of respiration rate, rhythm and depth; impairments such as apnoea, hyperventilation, irregular respiration, paradoxical respiration and bronchial spasm and as in pulmonary emphysema.
Coma	ICF-B110	General mental functions of the state of awareness and alertness, including the clarity and continuity of the wakeful state. Inclusions: functions of the state, continuity and quality of consciousness; loss of consciousness, coma, vegetative states, fugues, trance states, possession states, drug-induced altered consciousness, delirium, stupor
Control of voluntary movements	ICF-B760	Functions associated with control over and coordination of voluntary movements. Incl.: functions of control of simple voluntary movements and of complex voluntary movements, coordination of voluntary movements, supportive functions of arm or leg, right left motor coordination, eye hand coordination, eye foot coordination; impairments such as control and coordination problems, e.g. dysdiadochokinesia

Appendix 1. Continued

Adverse Event	***Code***	***Definition***
Deafness	ICD10-H91.9	Hearing loss, unspecified. Incl.: Deafness: NOS, high frequency, low frequency
Death		NOS
Depression	ICD10-F32	In typical mild, moderate, or severe depressive episodes, the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. Sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced and, even in the mild form, some ideas of guilt or worthlessness are often present. The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as loss of interest and pleasurable feelings, waking in the morning several hours before the usual time, depression worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Depending upon the number and severity of the symptoms, a depressive episode may be specified as mild, moderate or severe. Incl.: single episodes of: depressive reaction psychogenic depression reactive depression
Dislocation	ICF-B7150	Functions of the maintenance of structural integrity of one joint.
Dizziness	ICD10-R42	Dizziness and giddiness Incl.: Light-headedness, Vertigo NOS
Fainting	ICD10-R55	Syncope and collapse Incl.: Blackout, Fainting
Fatigue / Yawn	ICD10-R53	Malaise and fatigue
Flushing	ICD10-R23.2	Flushing, Excessive blushing
Fracture	ICD10-S12	Fracture of neck Incl.: cervical: neural arch, spine, spinous process, transverse process, vertebra, vertebral arch

Appendix 1. Continued

Adverse Event	***Code***	***Definition***
Headache	ICF-28010	Sensation of unpleasant feeling indicating potential or actual damage to some body structure felt in the head and neck.
Increased pain during movement	ICF-B2801	Sensation of unpleasant feeling indicating potential or actual damage to some body structure felt in a specific part, or parts, of the body during movement
Joint pain	ICD-M25.5	Pain in joint
Loss of movement	ICF-B710	Functions of the range and ease of movement of a joint. Inclusions: functions of mobility of single or several joints, vertebral, shoulder, elbow, wrist, hip, knee, ankle, small joints of hands and feet; mobility of joints generalized; impairments such as in hypermobility of joints, frozen joints, frozen shoulder, arthritis
Loss or reduced bladder control	ICF-B6200	Functions of voiding the urinary bladder. Incl.: impairments such as in urine retention
Loss or reduced bowel control	ICF-B5253	Faecal continence Functions involved in voluntary control over the elimination function
Migraine	ICD10-G43	Migraine
Muscle tenderness	ICD10-M79.1	Myalgia Excl.: myositis
Nausea	ICF-5350	Sensation of needing to vomit
Pain	ICF-B2801	Sensation of unpleasant feeling indicating potential or actual damage to some body structure felt in a specific part, or parts, of the body
Palpitations	ICD10-F45.3	Somatoform autonomic dysfunction
Panic attack	ICD10-F41	Disorders in which manifestation of anxiety is the major symptom and is not restricted to any particular environmental situation. Depressive and obsessional symptoms, and even some elements of phobic anxiety, may also be present, provided that they are clearly secondary or less severe.

Appendix 1. Continued

Adverse Event	***Code***	***Definition***
Radiating pain	ICF-B2803	Unpleasant sensation indicating potential or actual damage to some body structure located in areas of skin served by the same nerve root.
Severe sweating	ICD10-F45.3	Somatoform autonomic dysfunction
Skin rash	ICD10-L98.9	Disorder of skin and subcutaneous tissue, unspecified
Stroke	ICD10-I69	Sequelae of cerebrovascular disease
Transient Ischaemic Attack (TIA)	ICD10-G45	Transient cerebral ischaemic attacks and related syndromes Excl.: neonatal cerebral ischaemia
Vertigo	ICD10-H81.9	Disorder of vestibular function, unspecified
Visual disturbance	ICF-B210	Sensory functions relating to sensing the presence of light and sensing the form, size, shape and colour of the visual stimuli. Incl.: visual acuity functions; visual field functions; quality of vision; functions of sensing light and colour, visual acuity of distant and near vision, monocular and binocular vision; visual picture quality; impairments such as myopia, hypermetropia, astigmatism, hemianopia, colour-blindness, tunnel vision, central and peripheral scotoma, diplopia, night blindness and impaired adaptability to light
Vomiting	ICD10-R11	Vomiting
Abbreviations:	NOS	Not Otherwise Specified

APPENDIX 2

Appendix 2. Specified answers per group, severity and adverse event

	Duration	*No Adverse Event*			*Minor Adverse Event*			*Major Adverse Event*		
		Med	**MT**	**Pat**	**Med**	**MT**	**Pat**	**Med**	**MT**	**Pat**
Altered sensation ICF-B279	Hours	0%	0%	20%	100%	100%	80%	0%	0%	0%
	Days	0%	0%	20%	100%	90%	80%	100%	10%	0%
	Weeks	0%	0%	20%	0%	10%	0%	100%	90%	80%
Anxiety ICF-B152	Hours	0%	20%	20%	100%	80%	80%	0%	0%	0%
	Days	0%	20%	20%	100%	80%	80%	0%	0%	0%
	Weeks	0%	20%	20%	87.5%	70%	80%	25%	10%	0%
Breathing difficulties ICF-B440	Hours	0%	0%	20%	75%	50%	80%	25%	50%	0%
	Days	0%	0%	20%	0%	0%	0%	100%	100%	80%
	Weeks	0%	0%	20%	0%	0%	0%	100%	100%	80%
Coma ICF-B110	Hours	0%	0%	20%	0%	0%	0%	100%	100%	80%
	Days	0%	0%	20%	0%	0%	0%	100%	100%	80%
	Weeks	0%	0%	20%	0%	0%	0%	100%	100%	80%
Control of voluntary movements ICF-B760	Hours	0%	0%	20%	100%	80%	80%	0%	20%	0%
	Days	0%	10%	20%	75%	60%	60%	25%	30%	20%
	Weeks	0%	10%	20%	0%	0%	0%	100%	90%	80%
Deafness ICD10-H91.9	Hours	20%	0%	12.5%	80%	80%	62.5%	0%	20%	25%
	Days	20%	0%	12.5%	0%	10%	0%	80%	90%	87.5%
	Weeks	20%	0%	12.5%	0%	10%	0%	80%	90%	87.5%

Appendix 2. Continued

	Duration	*No Adverse Event*			*Minor Adverse Event*			*Major Adverse Event*		
		Med	**MT**	**Pat**	**Med**	**MT**	**Pat**	**Med**	**MT**	**Pat**
Death		0%	0%	0%	0%	0%	0%	100%	100%	100%
Depression ICD10-F32	Hours	25%	30%	20%	75%	50%	80%	0%	20%	0%
	Days	25%	30%	20%	75%	40%	60%	0%	30%	20%
	Weeks	25%	30%	20%	0%	10%	0%	75%	60%	80%
Dislocation ICF-B7150		0%	0%	20%	0%	0%	0%	100%	100%	80%
Dizziness ICD10-R42	Hours	12.5%	0%	20%	87.5%	90%	80%	0%	10%	0%
	Days	0%	0%	20%	37.5%	80%	80%	62.5%	20%	0%
	Weeks	0%	0%	20%	0%	10%	60%	100%	90%	20%
Fainting ICD10-R55	Hours	0%	0%	20%	75%	80%	80%	25%	20%	0%
	Days	12.5%	0%	20%	0%	0%	0%	87.5%	100%	80%
	Weeks	12.5%	0%	20%	0%	0%	0%	87.5%	100%	80%
Fatigue / Yawn ICD10-R53	Hours	100%	80%	100%	0%	20%	0%	0%	0%	0%
	Days	12.5%	30%	40%	87.5%	70%	60%	0%	0%	0%
	Weeks	12.5%	0%	20%	75%	80%	80%	12.5%	20%	0%
Flushing ICD10-R23.2	Hours	87.5%	100%	100%	12.5%	0%	0%	0%	0%	0%
	Days	0%	10%	20%	87.5%	90%	80%	12.5%	0%	0%
	Weeks	0%	0%	20%	75%	90%	80%	25%	10%	0%
Fracture ICD10-S12		0%	0%	20%	0%	0%	0%	100%	100%	80%

Appendix 2. Continued

	Duration	*No Adverse Event*			*Minor Adverse Event*			*Major Adverse Event*		
		Med	**MT**	**Pat**	**Med**	**MT**	**Pat**	**Med**	**MT**	**Pat**
Headache ICF28010	Hours	0%	20%	20%	100%	70%	80%	0%	10%	0%
	Days	0%	0%	20%	100%	90%	80%	0%	10%	0%
	Weeks	0%	0%	20%	75%	50%	20%	25%	50%	20%
Increased pain during movement ICF-B2801	Hours	0%	10%	20%	100%	90%	80%	0%	0%	0%
	Days	0%	10%	20%	100%	90%	80%	0%	0%	0%
	Weeks	0%	10%	20%	0%	0%	0%	100%	90%	80%
Joint pain ICD10-M25.5	Hours	12.5%	0%	20%	87.5%	100%	80%	0%	0%	0%
	Days	12.5%	10%	20%	87.5%	70%	80%	0%	20%	0%
	Weeks	12.5%	10%	20%	62.5%	30%	80%	25%	60%	0%
Loss of movement ICF-B710	Hours	0%	10%	40%	100%	90%	60%	0%	0%	0%
	Days	0%	0%	20%	100%	90%	80%	0%	10%	0%
	Weeks	0%	0%	20%	87.5%	50%	60%	12.5%	50%	20%
Loss or reduced bladder control ICF-B6200	Hours	0%	0%	20%	87.5%	40%	80%	12.5%	60%	0%
	Days	0%	0%	20%	0%	0%	0%	100%	100%	80%
	Weeks	0%	0%	20%	0%	0%	0%	100%	100%	80%
Loss or reduced bowel control ICF-B5253	Hours	0%	0%	20%	100%	40%	80%	0%	60%	0%
	Days	0%	0%	20%	0%	0%	0%	100%	100%	80%
	Weeks	0%	0%	20%	0%	0%	0%	100%	100%	80%
Migraine ICD10-G43	Hours	12.5%	0%	20%	87.5%	70%	80%	0%	30%	0%
	Days	12.5%	0%	20%	75.0%	60%	80%	12.5%	40%	0%

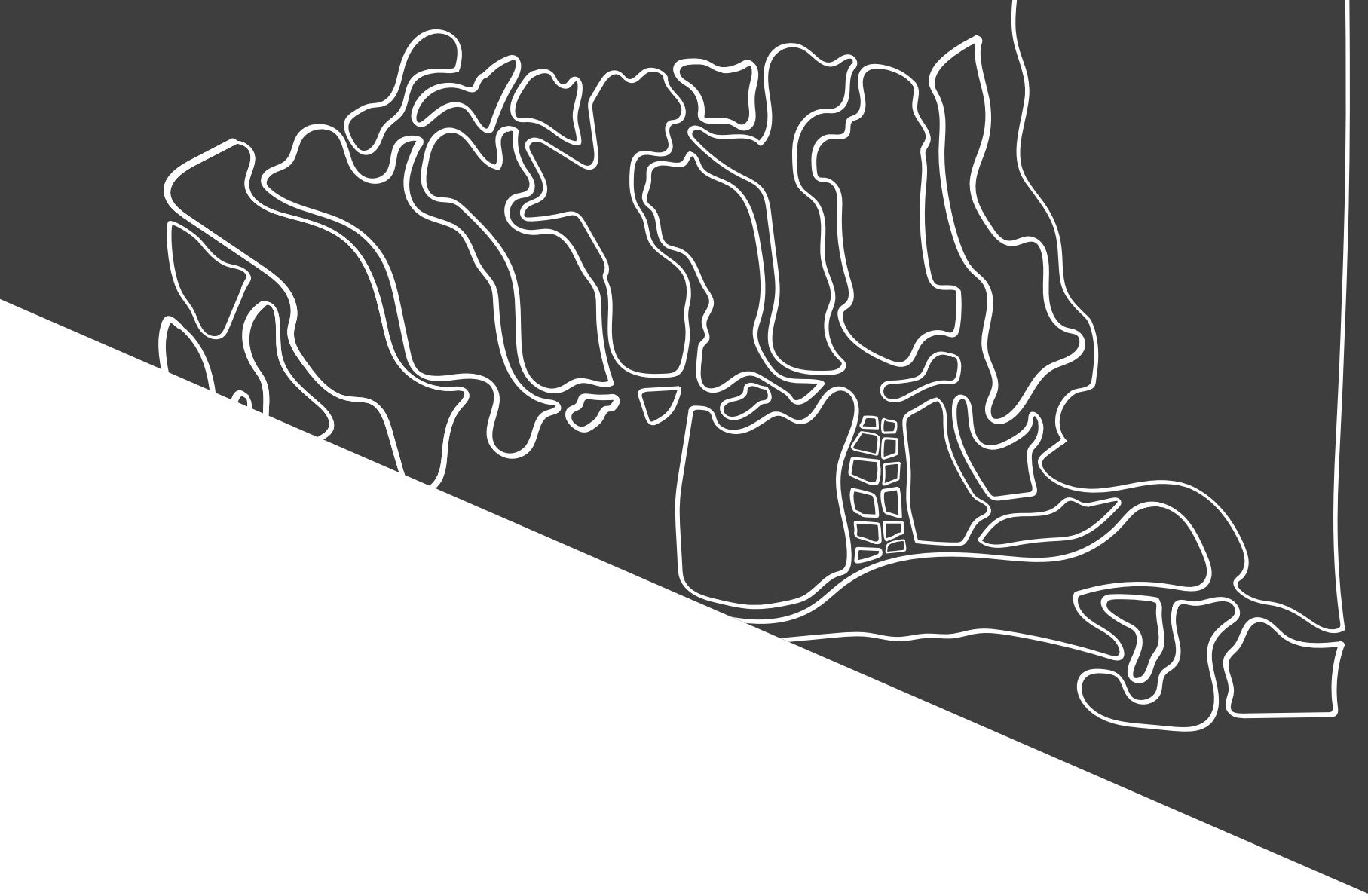
Appendix 2. Continued

	Duration	*No Adverse Event*			*Minor Adverse Event*			*Major Adverse Event*		
		Med	**MT**	**Pat**	**Med**	**MT**	**Pat**	**Med**	**MT**	**Pat**
Muscle tenderness ICD10-M79.1	Hours	100%	90%	100%	0%	10%	0%	0%	0%	0%
	Days	0%	10%	40%	100%	90%	60%	0%	0%	0%
	Weeks	0%	10%	20%	100%	90%	80%	0%	0%	0%
Nausea ICF-5350	Hours	0%	0%	20%	100%	100%	80%	0%	0%	0%
	Days	0%	0%	20%	100%	90%	80%	0%	10%	0%
	Weeks	0%	0%	20%	50%	70%	80%	50%	30%	0%
Pain ICF-B2801	Hours	0%	20%	20%	100%	80%	80%	0%	0%	0%
	Days	0%	0%	20%	100%	80%	80%	0%	20%	0%
	Weeks	0%	0%	20%	0%	0%	0%	100%	100%	80%
Palpitations ICD10-F45.3	Hours	0%	10%	20%	100%	70%	80%	0%	20%	0%
	Days	0%	10%	20%	87.5%	50%	40%	12.5%	40%	40%
	Weeks	0%	10%	20%	12.5%	0%	20%	87.5%	90%	60%
Panic attack ICD10-F41	Hours	12.5%	30%	20%	87.5%	50%	80%	0%	20%	0%
	Days	12.5%	30%	20%	75%	40%	60%	12.5%	30%	20%
	Weeks	12.5%	30%	20%	0%	0%	0%	87.5%	70%	80%
Radiating pain ICF-B2803	Hours	0%	0%	20%	100%	100%	80%	0%	0%	0%
	Days	0%	0%	20%	100%	90%	80%	0%	0%	0%
	Weeks	0%	0%	20%	0%	10%	0%	100%	100%	80%

Appendix 2. Continued

	Duration	*No Adverse Event*			*Minor Adverse Event*			*Major Adverse Event*		
		Med	**MT**	**Pat**	**Med**	**MT**	**Pat**	**Med**	**MT**	**Pat**
Severe sweating ICD10-F45.3	Hours	12.5%	30%	40%	87.5%	70%	60%	0%	0%	0%
	Days	12.5%	20%	20%	87.5%	80%	80%	0%	0%	0%
	Weeks	12.5%	10%	20%	50%	80%	80%	25%	10%	0%
Skin rash ICD10-L98	Hours	25%	10%	40%	75%	90%	60%	0%	0%	0%
	Days	12.5%	0%	20%	87.5%	100%	80%	0%	0%	0%
	Weeks	12.5%	0%	20%	87.5%	80%	80%	0%	20%	0%
Stroke ICD10-I69		0%	0%	0%	0%	0%	0%	100%	100%	100%
Transient Ischaemic Attack (TIA) ICD10-G45		0%	0%	20%	0%	0%	0%	100%	100%	80%
Vertigo ICD10-H81.9	Hours	12.5%	0%	20%	87.5%	90%	80%	0%	10%	0%
	Days	0%	0%	20%	37.5%	70%	60%	62.5%	30%	20%
	Weeks	0%	0%	20%	0%	0%	20%	100%	100%	60%
Visual disturbance ICF-B210	Hours	0%	0%	20%	75%	50%	40%	25%	50%	40%
	Days	0%	0%	20%	25%	30%	40%	75%	70%	40%
	Weeks	0%	0%	20%	0%	0%	20%	100%	100%	20%
Vomiting ICD10-R11	Hours	0%	0%	20%	100%	100%	80%	0%	0%	0%
	Days	0%	0%	20%	75%	70%	60%	25%	30%	20%
	Weeks	0%	0%	20%	0%	0%	0%	100%	100%	80%

Abbreviations: MED: Medical specialists, MT: Manual Therapists, PAT: Patients



ADVERSE EVENTS ASSOCIATED WITH THE USE OF CERVICAL SPINE MANIPULATION OR MOBILIZATION AND PATIENT CHARACTERISTICS: A SYSTEMATIC REVIEW

4

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ABSTRACT

Introduction: Cervical spinal manipulation (CSM) and cervical mobilization are frequently used in patients with neck pain and headache. Pre-manipulative cervical instability and arterial integrity tests appear to be unreliable in identifying patients at risk for adverse events. It would be valuable if patients at risk could be identified by specific characteristics during the preliminary screening. The objective was to identify characteristics of 1) patients, 2) practitioners, 3) treatment process and 4) adverse events (AE) occurring after CSM or cervical mobilization.

Method: A systematic search was performed in PubMed, Embase, CINAHL, Web-of-science, AMED, and ICL (Index Chiropractic Literature) up to December 2014.

Results: Of the initial 1043 studies, 144 studies were included, containing 227 cases. 117 cases described male patients with a mean age of 45 (SD 12) and a mean age of 39 (SD 11) for females. Most patients were treated by chiropractors (66%). Manipulation was reported in 95% of the cases, and neck pain was the most frequent indication. Cervical arterial dissection (CAD) was reported in 57% (P = 0.21) of the cases and 45.8% had immediate onset symptoms. The overall distribution of gender for CAD is 55% (n = 71) for female and therefore opposite of the total AE.

Discussion: Patient characteristics were described poorly. No clear patient profile, related to the risk of AE after CSM, could be extracted. However, women seem more at risk for CAD. There seems to be underreporting of cases. Further research should focus on a more uniform and complete registration of AE using standardized terminology.

INTRODUCTION

Cervical Spinal Manipulation (CSM) and cervical mobilization are frequently applied in patients with neck pain and headache.(Carlesso and Rivett, 2011) CSM is defined by the International Federation of Orthopedic Manipulative Physical Therapists (IFOMPT) as: "*A passive, high velocity, low amplitude thrust applied to a joint complex within its anatomical limit with the intent to restore optimal motion, function, and/ or to reduce pain*". (Beeton et al., 2010) Mobilization is defined as: "*Low-grade/velocity, small or large amplitude, passive movement techniques or neuromuscular techniques within the patient's range of cervical motion and control*".(Gross et al., 2004) In literature, the terms 'manipulation' and 'mobilization' are frequently interchanged or used to describe the same technique.(Mintken et al., 2008)

Both non-specific neck pain and cervicogenic headache are indications for manipulation or mobilization. Non-specific neck pain is a commonly experienced disorder with a lifetime prevalence of 70%.(Haldeman et al., 2009) Every year, 30% of the general population experiences neck pain, and 14% experience ongoing complaints for more than 6 months.(Vos, 2006) Cervicogenic headache is described by The International Headache Society (IHS) as to originate due to nociception in the cervical area. The incidence of cervicogenic headache is estimated to be 2.2%. (Antonaci and Sjaastad, 2011)

Adverse events (AE) or side effects following CSM and mobilization have been, although rarely, described in literature since 1907.(Carlesso et al., 2010; Cassidy et al., 2008; Roberts, 1907) An AE can be defined as the sequelae following a CSM that are medium to long term in duration, with moderate to severe symptoms, and of a nature that was serious, distressing, and unacceptable to the patient and required further treatment.(Carnes et al., 2010; Puentedura and O'Grady, 2015) Until recently, AE associated with CSM have only been described in case reports, retrospective case series, surveys from neurologists, or reviews.(Di Fabio, 1999; Ernst, 2002; Hurwitz et al., 1996) These reporting methods may lead to selection bias. Additionally, major AE seem to be reported more frequently than minor AE (also frequently described as: "side effects"). Side effects are defined as short term, mild in nature, non-serious, transient and reversible consequences of the treatment such as an increase in neck pain, headache, discomfort and fatigue.(Ernst, 2007, 2002; Puentedura et al., 2012)

Cervical Arterial Disorders (CAD) are described in multiple studies as major AE following CSM.(Carlesso et al., 2010; Ernst, 2007) CAD can cause stroke and have a described incidence of 2.6 to 2.9 per 100.000.(Giroud et al., 1994; Lee et al., 2006)

Mean age of patients is in the early 40's with a small majority for males (53 vs 47%). Furthermore, CAD appear to occur more in winters.(Arnold et al., 2006; Paciaroni et al., 2006; Touzé et al., 2003) One of the identified risk factors is recent infection, and this could explain this seasonal variance.(Thanvi et al., 2005) Other risk factors described are hypertension, migraine, connective tissue disorders and a recent history of cervical trauma.(Debette et al., 2011)

An extra cranial dissection of the internal carotid artery is diagnosed most often, followed by the vertebral artery.(Thanvi et al., 2005) Initial signs and symptoms of an internal carotid artery dissection are neck pain, headache, Horner's syndrome followed by retinal or cerebral ischemia.(Debette et al., 2011) Vertebral artery dissection frequently originates with cervical-occipital pain followed by vertigo, dysarthria, visual deficits, ataxia and diplopia. The dissimilarities in signs and symptoms of both dissections can be explained by the fact that the vertebral artery supplies the posterior part of the brain and the internal carotid artery the ventral part.(Blum and Yaghi, 2015)

As part of good practice, chiropractors and manipulative therapists perform a risk-benefit analysis prior to CSM. To perform a proper risk-benefit analysis, risk factors for AE related to CSM must be assessed. In pre-treatment risk-benefit analysis, the patient's medical history appears to be an important instrument to detect patients with a greater risk for AE.(Moore et al., 2005; Rushton et al., 2014; Thomas, 2016) Especially since pre-manipulative cervical instability and pre-manipulative cervical arterial tests seem to be invalid in identifying patients with a higher risk for AE.(N. Hutting et al., 2013; Nathan Hutting et al., 2013) It has been suggested that many AE can be prevented if a more detailed anamnesis and clinical reasoning is applied.(Puentedura et al., 2012; Rivett, 2004; Thomas, 2016) Therefore, patients' characteristics, in which risks for AE occur, could be of importance for the patient history as a part of the preliminary screening.(Taylor and Kerry, 2010) Previous reviews mostly had the objective to identify adverse events. Therefore, adverse events and outcome were described and marginally for patient and clinician details. To the authors' knowledge, detailed patient and clinician characteristics have never been inventoried.(Carlesso et al., 2010; Ernst, 2007, 2002)

This review will add information concerning (major) AE associated with CSM or mobilization, especially related to the type of AE, the emergent signs and symptoms, prevalence and specific patient characteristics. The objective of this review was to identify the detailed clinical characteristics of 1) patients, 2) the practitioner, 3) the

treatment process and 4) the AE occurring after CSM or cervical mobilization, in order to identify patients at risk during the preliminary CSM screening.

METHODS

A systematic literature search was performed in PubMed, Embase, CINAHL (Cumulative Index to Nursing and Allied Health), Web-of-science, AMED (Allied and Alternative Medicine Database) and ICL (Index Chiropractic Literature) up to December 2014. The concept search strategies as made by RK were reviewed and adjusted by a senior librarian. Full search strategies are provided in appendix 2.

Keywords used in the search string were: adverse effect, adverse event, complication, Stroke, Accident, Blood Vessel, Basilar Artery, Carotid Artery, Vertebral artery, Risk Factor, Neck, Injury, Cervical, Manipulation, Chiropractic, Osteopathic, Adult, Retrospective Study, Case Report and Retrospective case survey. Additional studies were identified by hand searching in journals and reference lists and related articles (PubMed function). A grey literature search was not included.

Prior to the review process, inclusion and exclusion criteria by two of the authors were set. Only published case reports or surveys were included, when they met following criteria: published before 2015, written in English, Dutch, German or Norwegian, describing adult patients with AE following treatment with CSM or mobilization. Articles were excluded if: (1) no AE was described; (2) described that the patient received during the same session other spinal manipulation besides CSM or mobilization, or during the same session; (3) patient characteristics were not described; (4) the article was a systematic or literature review; (5) patients were not adults; or (6) articles in any other language than English, Dutch, German or Norwegian.

Only case reports, case series or surveys were included, for in those reports the most details are described. RCT's and reviews do not describe specific patient and clinician information.(Pitrou et al., 2009; Tsang et al., 2009)

At the start, two authors (RK and MS) executed the whole assessment process together on three articles. This was in order to minimize differences in interpretation. The summary of the review process is described in- and exclusion criteria. After this training session, the same two authors ran through the review process independently and discussed the results of each step in consensus meetings, prior to the next step. In the first step, all titles in the primary search were screened on

inclusion criteria and duplicates. During the second step of the review process, full-text articles were independently screened and analyzed on inclusion and exclusion criteria. Subsequently, authors filled in a data-extraction form. During the consensus meetings, after each step in the review process, disagreements were discussed and resolved. The summary of the review process is described in Figure 1.

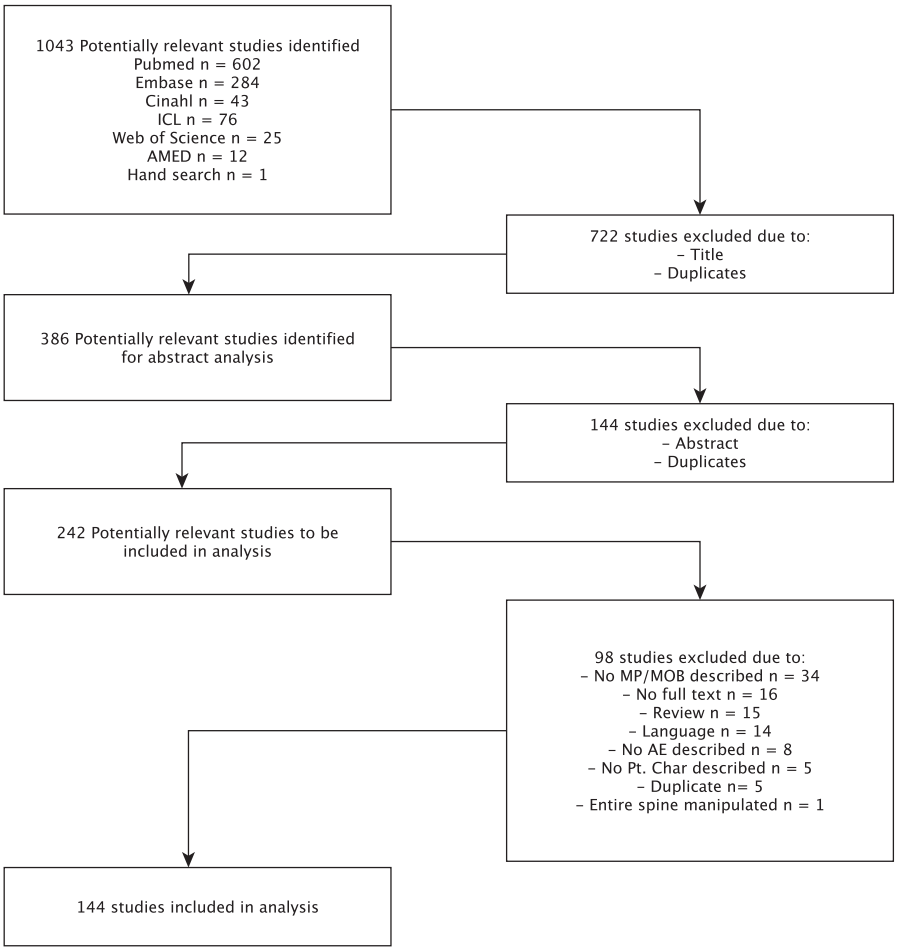

Figure 1. PRISMA flowchart: Selection process of relevant studies

During the review process, PRISMA guidelines, an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses, were followed, although methodological quality of the case reports was not appraised.(Moher et al.,

2016) No risk of bias criteria were available for case reports, case series or surveys. Therefore, this was not assessed.

Following general epidemiological parameters were used in the inventory: gender, age, region, treating profession of the health care professional, profession of patient, sport, level of education, level of income, leisure time, anxiety, and depression. Also, specific parameters like: indication, time to onset of symptoms, technique used, type of AE, signs /symptoms, contra indications, precautions and risk factors were noted when present or absent in a patient. Parameters used for the data-collection were based on the IFOMPT framework. This framework is a consensus document for best practice examination of the cervical region prior to cervical manual interventions. (Rushton et al., 2014) An explicit differentiation was made between types of AE (pathologies like vascular dissection or fracture) and signs and symptoms (i.e. neck pain or dizziness) since they are two substantially different elements as one is the result of the other.(Rushton et al., 2014) The Mann-Whitney test was used to analyze differences in gender of patients with Cervical Arterial Disorders (CAD).

RESULTS

The result of our search is presented in figure 1. A total of 1043 potentially relevant studies were identified. After comparing and discussing the results, 722 studies were excluded on title or duplicates. Of the remaining 386 studies, the same protocol as in round 1 was applied and 144 studies were excluded based on abstract and duplicates. The remaining 242 potentially relevant full text studies were analyzed individually (RK and MS). Results were compared and discussed until consensus. Of those 242 a total of 98 articles were excluded due to: no full text available (n=16), no CSM or mobilization described (n=34), review (n=15), language (n=14), no AE described (n=8), no patient characteristics described (n=5), duplicate (n=5) and entire spine manipulated (n=1). A total of 227 cases reported in 144 articles left, were included and analyzed. Of the included cases 66.1% were published in case reports, 28.2% in retrospective case series and 5.7% in surveys.

Only a few parameters were well described in the reported cases (Figure 2). For the parameters Precautions, Risk factors CAD Risk factors Upper Cervical Instability (UCI) and Contraindications the mean percentage of parameters described in the IFOMPT statement was calculated.(Rushton et al., 2014) Detailed synopsis per case is described in Supplemental Table I.

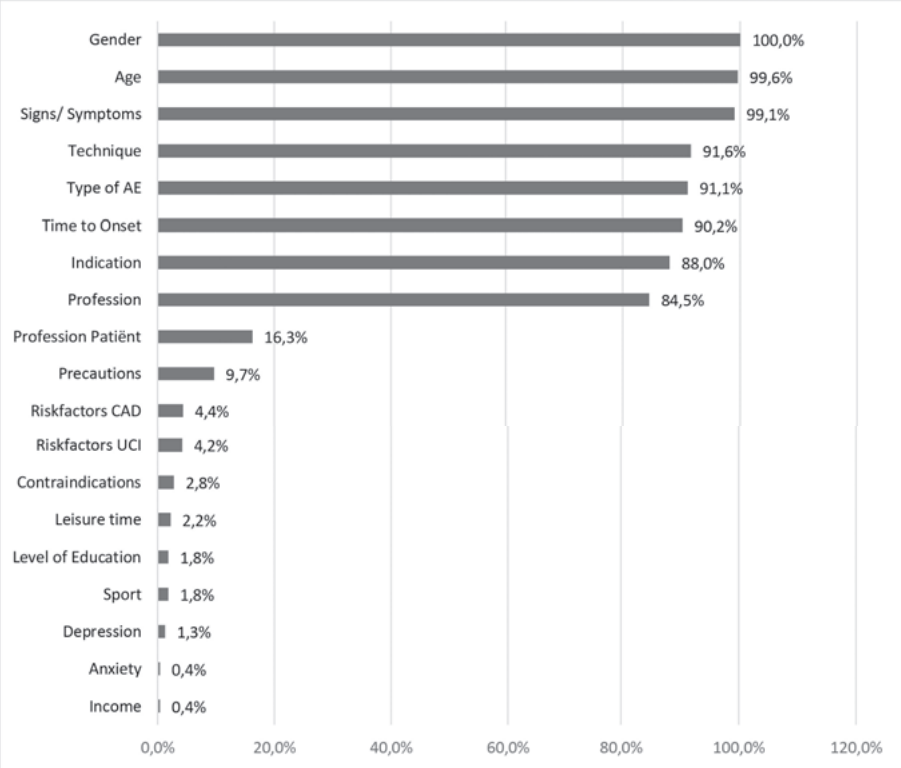

Figure 2. Described parameters per case in percentages

Of the 227 cases, 117 (51.5%) were male. The mean (SD) age of all cases was 42 (12) years. However, the majority of male patients was approximately 5 years older with a mean age of 44.74 (SD 11.91, and a total range 17-87 years), while for female patients mean age was 39.22 (SD 11.12, Range 21-73).

TYPE OF PROFESSION PROVIDING CSM

The majority of patients with reported major AE were treated by chiropractors (65.6%), 5.3% by non-clinicians, 4.8% by osteopaths, 3.1% by physical therapists, 2.6% by other medical professions (e.g. general practitioner), 2.2% (= 5 cases) by self-treatment, 0.4% by manual therapists. For 15.9% of the cases the profession was not described. In Figure 3 a cross table combining health profession and region is provided.

TYPE OF MANIPULATION PROVIDED

Manipulation was the most frequently reported technique (95.2%). In 62.6% of the cases, patients received a non-specified manipulation (i.e. impulse and/or direction was not specified), 26.9% a rotation manipulation, 2.6% a traction manipulation and 3.1% another type of manipulation. In 1.7%, patients were treated with mobilizations. For 3.1% of the patients the technique was not described.

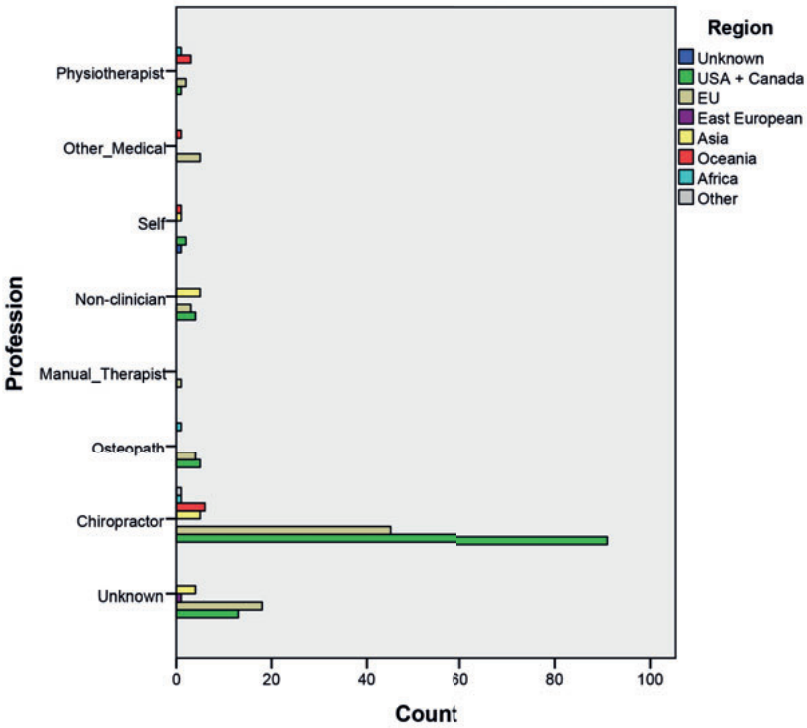

Figure 3. Profession per region

INDICATIONS FOR MANIPULATION

Indications for the use of CSM were only described in 87.6% of the patient cases. Neck pain or stiffness was the most commonly reported indication for 147 of the 227 (64.8%) patients (77 males). Headache was the next frequent indication in 40 of the 227 (17.6%) patients (27 females). Interestingly, dizziness was the reported indication for CSM in 2 female patients, and 31 patients (22 males) had other indications. For the final 28 patients (10 males) there was no treatment indication reported.

TYPE OF AE

The most commonly reported type of AE was cervical arterial dissection (CAD) (57% of the cases), and this was a combination of all reported vascular dissections. The overall distribution of gender for dissections was 55% (n= 71) for female and 45% (n= 58) for male. As shown in Figure 4, the most frequently reported specific type of AE was the Vertebral Artery dissection. Of all vertebral artery dissections in our sample (53 cases), 65.9% were female and 30 male cases (36.15%) were counted.

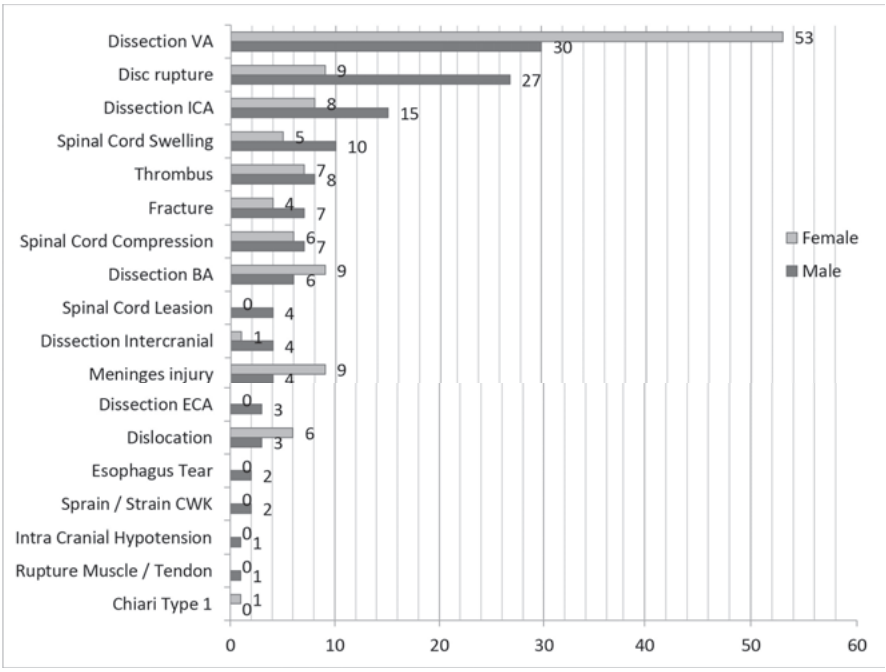

Figure 4. Type of AE by gender

TYPE OF SIGNS AND SYMPTOMS ASSOCIATED WITH AE

The most frequently described symptom was a disturbance of control of voluntary movements (104), followed by altered sensation (97), pain (82), paresis (71), visual disturbance (54), nausea (48), headache (47), vomiting (44), and vertigo (43). The full enumeration is shown in figure 5.

ONSET OF SIGNS AND SYMPTOMS

Immediate onset of the signs and symptoms was reported in 45.8% of the cases, and of these, 53% were male and 47% were female. The majority of symptoms had

an onset within 1 week with 84.5% (83.7% Male and 87.2% Female). Overall, in 2.6% symptoms started within 1-2 weeks and in 1.8% in took more than 2 weeks. In 23 cases (10.2%) time to onset was not described.

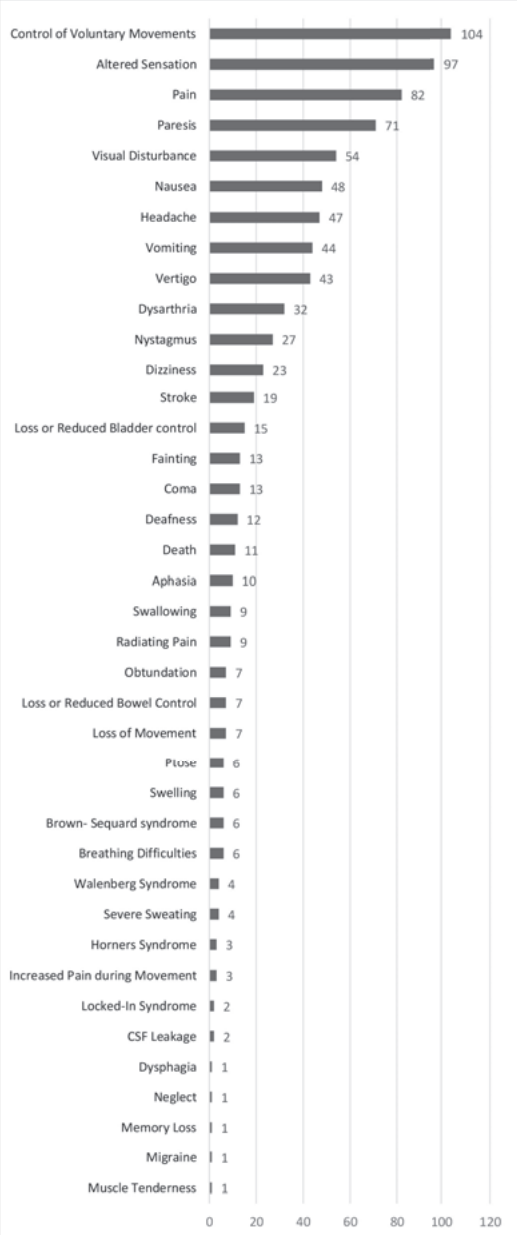

Figure 5. Signs and Symptoms - Frequency table

DISCUSSION

The results of this review identified some of the clinical characteristics of patients in which AE occurred after CSM or mobilization. This review showed that women seem to be more at risk for CAD however, no clear patient profile could be extracted from the reported parameters. Gender was the only characteristic reported in all cases, and age was reported in all but one of the 227 included cases. The results show that gender and age characteristics were consistent with other literature.(Blum and Yaghi, 2015; Puentedura et al., 2012) Therefore, from the reported literature reviewed, one could conclude that a person (male or female almost equal) around their 40's is most at risk.(Blum and Yaghi, 2015; Kosloff et al., 2015) Other patient related details were marginally described, if stated at all, therefore, we were unable to draw any conclusions on this. This review also identified that the majority of AE patients were treated by chiropractors. Neck pain or stiffness was the primary indication, and manipulation, rather than mobilization, was the technique most often used. The most frequently reported AE was vertebral artery dissection, and the loss of control of voluntary movements was the most often reported symptom with the majority of symptoms onset within a week after the intervention.

Despite the fact that clinical characteristics such as smoking, cervical trauma, recent infection, hypertension, migraine, low cholesterol and low body mass index are well described as possible risk factors for all AE dissections in the literature,(Debette, 2014; Engelter et al., 2013) we found them scarcely described in the reported cases. It seems unlikely that the limited description of these items is due to difference in guidelines, procedures and standards, as the majority of items in those documents should be overlap and therefore, cannot be the explanation for the large absence of data. It could be that they were not described because they were not present in the patients in the published cases. Or it might be that the manipulating professionals did not see the need to report or were unaware of these items. Another explanation could be that although not specifically inventoried, both reviewers (RK and MS) noted that a substantially number of publishing authors had a medical background (i.e. neurologist) and were more focused on the AE treatment strategy and recovery after hospitalization. As they have a different scope, aim and body of knowledge, they may have reasonably described other items. Similar calls to improve quality of case reports have been done in adjacent medical fields.(Kaszkin-Bettag and Hildebrandt, 2012) In 2013 the CARE statement was published to guide transparency and accuracy of case reports as well as to improve the quality of case reports. (Gagnier et al., 2014; Richason et al., 2009)

In the published case reports, we found most the frequently described the type of AE to be cervical arterial dissection (CAD) (57% of the cases). The overall distribution of gender for dissections was 55% (n= 71) for female and 45% (n= 58) for male. Although no statistically significant difference was found in our review, it contrasts with other studies which were large cohort studies and included mostly 'non-manipulative' CAD patients. In those studies, male cases were more prevalent.(Debette et al., 2009; Engelter et al., 2013) This difference seems hard to explain anatomically and may simply be a factor of greater reporting of case studies involving male patients suffering AEs after CSM. Metso et al described that a CAD was more common in males (57.6% vs 43.3%).(Metso et al., 2012) However, he also noted that in the CAD group, more female patients experienced clinical signs and symptoms than men after chiropractic manipulation.

In accordance with other literature including the non-manipulative population, the majority of patients in our review were slightly younger than 45 years.(Kosloff et al., 2015) As in other studies, the vertebral artery dissection was the most frequently described type of AE after CSM.(Biller et al., 2014; Ernst, 2007; Leon-Sanchez et al., 2007) Remarkably, in the general European population of patients with CAD, carotid dissections are more common than VAD with a ratio of 1.7 to 1.(Lee et al., 2006) A commonly described explanatory mechanism is the stretch in the vertebral artery in the manipulative position of the cervical spine. Approximately 50% of the cervical rotation occurs in the atlanto-axial joint. The other 5 most frequently described types of AE (Figure 3) were in accordance with a comparable previous study.(Puentedura et al., 2012)

Considering the fact that CAD is the most frequently occurring AE, it may be disconcerting that neck pain or stiffness was found to be the most frequent indication. This is because neck pain is also one of the main symptoms of CAD. Church et al. therefore described neck pain as the potential confounder and it is possible that patients attend for treatment with a pre-existing arterial dissection (neck pain and headache being the pre-ischaemic symptoms) and that CSM had not caused the neurovascular symptoms that would have naturally developed regardless of their intervention.(Church et al., 2016) Furthermore, in the most described cases, no (suggestion for) causality was described. Although evidence is thin, no causal relationship seems to exist between CSM and CAD.(Church et al., 2016). Therefore, an inventory with indications of possible causations would be unreliable, as it would be based on assumptions by judgement, and not founded with criteria of causation. Therefore, this review does not contain any description or

suggestions of causation related to the artery dissections. Taken together, clinicians are strongly advised to incorporate vascular examination (i.e. blood pressure) in their risk assessment and vascular pathologies in their clinical reasoning process, prior to considering CSM for their patient.

Perhaps the most serious AE following CSM, and often mentioned in debates, guidelines or procedures, is death. It was described in only 11 of the 227 cases (4.8%) with major AE. As most of the AE were due to arterial dissections, these numbers are in concordance with the survival rates in other literature.(Biller et al., 2014; Rushton et al., 2014) Recovery report or health status was not inventoried during this review.

Most of the included cases involved chiropractors or chiropractic manipulations (65.6%), and other authors found similar percentages as mentioned in Figure 5.(Ernst, 2007; Puentedura et al., 2012) Explanations might be, that CSM are more frequently used by chiropractors, that there may be a greater readiness on the part of authors to publish case reports of AE involving chiropractors, more people at risk seek help from chiropractors or that they have a more hazardous way of performing their manipulations.(Di Fabio, 1999)

Underreporting of AE after CSM may be the case, when comparing the reported cases to calculated incidence rates. VAD has a reported annual incidence rate of 1 - 1.5 per 100.000 while Internal Carotid Artery Dissection (ICAD) has a reported annual incidence rate of 2.6 - 3 per 100.000.(Micheli, 2010; Schievink et al., 1994) In 2008, Cassidy reported that 7.8% of his population had visited a chiropractor within 7 days, whereas Engelter found a 6.9% rate.(Cassidy et al., 2008; Engelter et al., 2013) As of July 1st 2014, there were approximately 318.857.056 US citizens, and using the above incidence rates, it would mean approximately 220 VAD patients annually with recent manipulation. (U.S. Department of Commerce 2014) Taken into account that the first case in this review was reported in 1907, the 227 included cases (worldwide) in such a long period suggests that it must be the proverbial tip of the iceberg.

This review has some limitations. Interpretation and classification of described signs and symptoms caused considerable debate between the reviewers (RK and MS). Even though we used the ICF and ICD criteria, there was an overlap in definitions, for pain, radiating pain, increased pain during movement and headache. The broad possibility of interpretation of definitions could be an issue in the differences in interpretation of the data, for example: Control of voluntary movements (ICF-B760).

Loss of muscle strength or weakness was included is this parameter, whereas other studies did not.(Puentedura et al., 2012)

Another note of caution is due here since appraising the quality of case reports is difficult, as no validated tool is available. The authors decided not to create a tool to appraise methodological quality, for instance based on the CARE statement, for case reports. A case report either contains or does not contain information, so methodological quality is less relevant.

Furthermore, in the literature manipulation terminology is known to be interchanged. Because we included both, manipulation and mobilization, this issue should not affect the initial search results of this study.(Mintken et al., 2008) It could however have influenced the results of techniques used, as 62.6% of the included patients received a non-specified manipulation. Although in many of those cases, patients mentioned that there was a sudden fast impulse, followed by a crack, one could question these outcomes. However, as far as we know this is the largest cohort describing AE associated with CSM or mobilization, especially related to the sort, prevalence and patient characteristics.

SUMMARY AND RECOMMENDATIONS

To gain more insight in incidence rates and patient characteristics in order to identify patients at risk, the authors recommend that manipulating professionals report their AE cases themselves. Alternatively, they should report as thoroughly as possible, all the patient characteristics, in co-operation with the involved physician. For those future reports, we recommend incorporation of the advice of Mintken et al complemented with Puentedura's advice in the CARE template.(Gagnier et al., 2014; Mintken et al., 2008; Puentedura and O'Grady, 2015) We also suggest the use of concrete medical terminology, preferably based on the International Classification of Diseases (ICD) or International Classification of Functioning (ICF) as published by the World Health Organization (WHO). Furthermore, we urgently appeal the professional organizations to communicate clearly to their members where and what to report and facilitate a clear protocol based on the above mentioned.

Disclosures: None.

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APPENDICES

APPENDIX 1: SPECIFIED CASE RESULTS SORTED ALPHABETICALLY PER STUDY.

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Agarwal	2004	1	Male	37	3, 5	3, 6, 9, 21, 26	Manipulation Rotation
Ahmad	1999	2	Female	28	4	0	Manipulation Not Described
Ahmad	1999	2	Male	50	1	0	Manipulation Not Described
Albuquerque	2011	3	Female	39	3	9, 25, 24, 6, 35	Manipulation Not Described
Albuquerque	2011	3	Female	33	3	6, 8, 9, 26	Manipulation Not Described
Albuquerque	2011	3	Male	30	3, 4	9, 14, 34, 35	Manipulation Not Described
Albuquerque	2011	3	Female	50	3	7, 26, 35	Manipulation Not Described
Albuquerque	2011	3	Female	39	3, 4	6, 8, 24, 25	Manipulation Not Described
Albuquerque	2011	3	Male	54	1, 3, 4	26, 36	Manipulation Not Described
Albuquerque	2011	3	Female	41	3	8	Manipulation Not Described
Albuquerque	2011	3	Male	53	1	35, 36	Manipulation Not Described
Albuquerque	2011	3	Female	73	3, 4	30	Manipulation Not Described

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Albuquerque	2011	3	Male	38	3	6, 26	Manipulation Not Described
Albuquerque	2011	3	Female	34	3	6, 8, 14	Manipulation Not Described
Albuquerque	2011	3	Male	48	3	6, 24, 25	Manipulation Not Described
Albuquerque	2011	3	Female	39	3	9, 24, 25	Manipulation Not Described
Beatty	1977	1	Male	37	1	33, 35, 36	Manipulation Rotation
Beck	2003	1	Female	40	10	37	Manipulation Rotation
Bekavac	2006	1	Male	49	5	7, 9	Manipulation Not Described
Bertino	2012	1	Female	37	3	6, 7, 24, 26, 29	Manipulation Rotation
Braun	1987	1	Male	47	3	7, 26, 35, 39	Manipulation Not Described
Braune	1991	1	Male	59	1	8, 9, 14, 26, 30, 35	Manipulation Rotation
Braus	1991	1	Female	26	3	7, 8, 26, 39	Manipulation Not Described
Braus	1991	1	Male	60	14	7, 30, 35	Manipulation Not Described
Brownson	1986	1	Female	26	3	1, 4, 6, 24, 25, 26	Manipulation Rotation
Brownson	1986	1	Male	46	4	1, 6, 7, 26	Manipulation Rotation
Caprieaux	2012	1	Male	37	5	32	Unknown

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Cerimaqic	2007	1	Male	46	3	14, 24, 25, 26, 39	Manipulation Not Described
Chakraverty	2011	1	Male	50	13	8, 9, 38	Manipulation Rotation
Chen	2011	1	Male	33	10	14	Unknown
Chen	2006	1	Male	28	3	6, 7, 8, 26, 30	Manipulation Not Described
Christensen	2003	1	Male	39	0	6, 8, 14, 26, 30, 35	Manipulation Rotation
Christian	2004	1	Male	39	3	14, 22, 24, 25, 26, 33	Manipulation Traction
Chung	2002	1	Male	46	12	8, 16, 26	Manipulation Rotation
Citisli	2012	1	Male	33	11, 12	35	Manipulation Not Described
Cook	1991	1	Female	33	0	6, 8, 24, 25, 26, 35, 39	Manipulation Rotation
Cortazzo	1998	1	Male	36	3	6, 24, 25	Manipulation Not Described
Dandamundi	2012	1	Male	63	14	8, 20, 30	Manipulation Not Described
Daneshmend	1984	1	Male	31	14	7, 8, 30, 33, 35	Manipulation Rotation
Davis	1985	1	Male	56	17	8, 26, 35	Manipulation Not Described
Davis	1985	1	Male	64	12	8, 9, 20, 35	Manipulation Not Described
Degirmenci	2012	1	Male	32	0	8, 24, 25, 33, 26, 35, 40	Manipulation Not Described

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Destee	1989	1	Male	31	10,11	8, 20, 21, 22, 26, 35	Manipulation Not Described
Deveraux	2000	1	Female	34	3	7	Manipulation Not Described
Domenicucci	2007	1	Female	52	17	9, 26, 38	Manipulation Not Described
Donovan	2007	1	Female	32	10	1, 5, 7, 13, 14, 26, 25, 37	Mobilization Other
Donzis	1997	1	Female	39	0	5, 7	Manipulation Not Described
Dunne	1987	1	Male	43	3	4, 6, 7, 14, 24, 32, 33, 39	Manipulation Rotation
Easton	1977	1	Female	38	3	32	Manipulation Other
Easton	1977	1	Female	48	0	5, 14, 24, 26, 33	Manipulation Not Described
Easton	1977	1	Female	44	3, 4	7, 14, 35, 40	Manipulation Not Described
Epstein	2013	1	Male	45	11, 17	9, 35	Manipulation Traction
Fast	1987	1	Female	27	3	4, 8, 24, 25, 29, 35, 39	Manipulation Not Described
Foreman	2013	1	Male	59	13	21, 26	Manipulation Not Described
Frisoni	1991	1	Male	42	0	3, 7, 8, 9, 10, 26, 33, 35	Manipulation Not Described

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Frisoni	1991	**1**	Female	39	3	8, 9, 24, 25, 26, 35, 39, 45, 48	Manipulation Not Described
Frisoni	1991	1	Female	49	0	6, 7, 24, 25, 26, 39	Manipulation Not Described
Fritz	1984	1	Female	60	0	6, 7, 24, 25, 26, 39	Manipulation Rotation
Fritz	1984	1	Female	21	14	5, 6, 25, 26, 30	Manipulation Rotation
Fritz	1984	1	Male	63	14	1, 5, 6, 7, 26, 30, 39	Manipulation Rotation
Frumkin	1990	1	Female	40	4	5, 8, 26, 33, 35, 40	Manipulation Rotation
Frumkin	1990	1	Male	33	3	5, 7, 8, 9, 14, 25, 26	Manipulation Rotation
Frumkin	1990	1	Female	40	3	6, 7, 8, 9, 24, 25, 26	Manipulation Rotation
Frumkin	1990	1	Male	28	0	6, 7, 8, 25, 26, 30, 39	Manipulation Rotation
Gamer	2002	1	Male	37	3	6, 8, 25, 26, 39	Manipulation Not Described
Gamer	2002	1	Male	37	1	8, 9, 26, 45	Manipulation Not Described
Gittinger	1986	1	Male	44	2	7, 14	Manipulation Not Described
Goufeia	2007	1	Female	41	3, 4	6, 8, 14, 16, 26, 35, 39	Manipulation Not Described
Goufeia	2007	1	Female	68	0	8, 35	Manipulation Traction
Goufeia	2007	1	Male	34	13	8, 26	Manipulation Not Described

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Grayson	1987	1	Male	45	0	7, 9, 14, 35	Manipulation Other
Hamann	1993	2	Female	30	3	4, 25	Manipulation Traction
Hamann	1993	2	Male	38	1, 3	4	Manipulation Rotation
Hamann	1993	2	Female	31	3	5, 9	Manipulation Traction
Hamann	1993	2	Female	31	3, 4	9, 14, 24, 25, 26, 39	Manipulation Traction
Hartel	2011	1	Male	56	6, 7	3, 8, 35	Manipulation Not Described
Heffner	1985	1	Female	55	0	13, 26	Manipulation Not Described
Heiner	2009	1	Female	38	13	8, 26, 35	Manipulation Not Described
Hillier	1998	1	Female	38	3	6, 9, 24, 45	Manipulation Other
Hoffelner	2009	1	Female	30	14	9, 33, 41	Manipulation Not Described
Horn	1983	1	Male	34	3	4, 5, 25, 41	Manipulation Not Described
Hsieh	2010	1	Female	61	11, 13	8, 9, 26, 35, 38	Manipulation Not Described
Huffnagel	1999	2	Male	35	3	4, 6, 7, 25, 35	Manipulation Rotation
Huffnagel	1999	2	Female	40	3	6, 7, 26, 33, 35, 36, 39, 48	Manipulation Rotation
Huffnagel	1999	2	Female	27	3	9, 34, 35, 41	Manipulation Rotation

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Huffnagel	1999	2	Female	29	3	6, 25	Manipulation Rotation
Huffnagel	1999	2	Female	29	3	6, 8, 25, 33, 35	Manipulation Rotation
Huffnagel	1999	2	Female	35	3	24, 25, 26, 29, 33, 35	Manipulation Rotation
Huffnagel	1999	2	Female	31	3	3, 6, 16, 24, 25	Manipulation Rotation
Huffnagel	1999	2	Female	34	3	6, 7, 9, 24, 25, 35, 39	Manipulation Rotation
Huffnagel	1999	2	Male	35	1	7, 14, 25	Manipulation Rotation
Huffnagel	1999	2	Male	46	1	7, 14, 33, 36	Unknown
Jang	2012	1	Male	49	14	7	Manipulation Not Described
Jatuzis	2012	1	Female	26	3	14	Manipulation Not Described
Jay	2003	1	Female	26	3	7, 14	Manipulation Not Described
Jentzen	1987	1	Male	51	3	1, 3, 6, 7, 24, 25, 30, 32	Manipulation Not Described
Jeret	2001	1	Male	34	10	5, 9, 14	Manipulation Not Described
Johnson	1993	1	Male	26	0	6, 7, 8, 24, 25, 26, 39	Manipulation Rotation
Jumper	1996	1	Male	87	14	7	Mobilization Not Described
Kehr	1989	1	Female	30	6	9, 14 , 20	Manipulation Rotation

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Kewalramani	1982	2	Female	23	6	8, 9, 14, 21, 26, 35	Manipulation Not Described
Kewalramani	1982	2	Male	46	17	8, 9, 21, 22, 26, 35	Manipulation Not Described
Kewalramani	1982	2	Male	62	17	8, 9, 21, 22, 26, 35	Manipulation Not Described
Khan	2005	1	Male	56	1	7, 48	Unknown
Kraft	2001	1	Male	43	8	9	Manipulation Not Described
Krieger	1990	1	Female	37	3	5, 44	Unknown
Krieger	1990	1	Female	39	3	7, 8, 9, 33, 35	Unknown
Kristine	2001	1	Female	34	0	26, 30, 42	Manipulation Not Described
Kuitwaard	2008	1	Male	42	3	6, 7, 8, 26, 33	Manipulation Other
Kurbanyan	2008	1	Female	46	10	7, 9, 14, 20	Manipulation Rotation
Kusnezov	2013	1	Female	29	10	14, 24, 25	Manipulation Rotation
Latimer	1991	1	Male	24	15	9, 33	Manipulation Traction
Lennington	1980	1	Male	53	2	9, 41	Manipulation Not Described
Leong	2001	1	Female	47	16	7, 9, 14, 26, 40	Manipulation Not Described
Leon-Sanchez	2007	1	Female	27	14	1, 6, 8, 14, 24, 25, 32, 33, 34	Manipulation Rotation

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Leweke	1999	1	Female	34	3	5, 7, 9, 14, 24, 25	Manipulation Not Described
Lewis	1992	1	Female	61	6	26, 35	Manipulation Not Described
Lewis	1992	1	Male	60	0	8, 26, 35	Manipulation Not Described
Liao	2007	1	Male	66	7	8, 21, 26, 35	Manipulation Not Described
Lidder	2010	1	Male	64	13	8, 9, 26	Manipulation Not Described
Lipper	1998	1	Female	58	13	8, 9, 26	Manipulation Rotation
Lopez-Gonzalez	2011	1	Male	45	7	26, 35	Manipulation Not Described
Malone	2002	2	Male	38	11, 17	8, 9, 26	Manipulation Other
Malone	2002	2	Male	45	11	8, 9	Manipulation Not Described
Malone	2002	2	Female	41	11	9, 26	Manipulation Not Described
Malone	2002	2	Female	35	11	26, 38	Manipulation Not Described
Malone	2002	2	Female	48	11	8, 9	Manipulation Not Described
Malone	2002	2	Male	59	11	8, 9, 26	Manipulation Not Described

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Malone	2002	2	Male	38	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Male	44	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Female	68	17	9	Manipulation Not Described
Malone	2002	2	Female	45	13	9	Manipulation Not Described
Malone	2002	2	Female	43	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Male	53	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Male	57	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Female	39	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Male	61	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Male	31	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Male	49	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Female	43	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Male	52	11	8, 9, 26	Manipulation Not Described

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Malone	2002	2	Male	51	11	8, 9, 26	Manipulation Not Described
Malone	2002	2	Male	55	11	8, 9, 26, 38	Manipulation Not Described
Malone	2002	2	Male	58	11	4, 5, 8, 9, 26	Manipulation Not Described
Mas	1987	2	Female	27	3	1, 6, 7, 26, 33, 40	Manipulation Not Described
Mas	1987	2	Female	47	3, 4	7, 24, 39	Manipulation Not Described
Mas	1989		Female	35	3	8, 30,32, 33,35, 46	Manipulation Not Described
Mathews	2006	1	Female	51	10	7	Manipulation Not Described
Miley	2008	1	Male	39	3	7, 8, 24, 25, 33, 36	Manipulation Not Described
Misra	2001	1	Male	30	13	4, 8, 21, 26	Manipulation Rotation
Morelli	2006	1	Male	49	18	1, 14	Manipulation Rotation
Morton	2012	1	Female	31	1	7, 9	Manipulation Not Described
Mueller	1976	1	Female	43	0	6, 7, 24, 26, 33, 39	Manipulation Not Described
Mueller	1976	1	Female	28	6	3, 8, 24, 26, 35	Manipulation Not Described

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Mueller	1976	1	Male	38	3	5, 7, 9, 14, 24, 25, 35	Manipulation Not Described
Murphy	2006	1	Male	38	11	8, 9	Manipulation Not Described
Murthy	1988	1	Male	40	1	7, 33, 40	Manipulation Rotation
Nadgir	2003	1	Male	43	1	8, 14, 33, 43	Manipulation Not Described
Neetu	2006	1	Male	55	13	8, 9, 10, 21, 26, 35, 38	Manipulation Not Described
Nyberg-Hansen	1978	1	Female	38	3	3, 7, 30	Manipulation Not Described
Oehler	2003	1	Female	31	3	7, 8, 26, 35	Unknown
Oppenheim	2005	2	Male	54	11	35	Manipulation Not Described
Oppenheim	2005	2	Female	71	7	26, 35	Manipulation Rotation
Padua	1996	2	Male	67	11	8, 13, 26, 35	Manipulation Not Described
Padua	1996	2	Male	56	11	8, 26, 35	Manipulation Not Described
Padua	1996	2	Male	56	11	8, 26	Manipulation Not Described
Padua	1996	2	Male	62	0	8, 26	Manipulation Not Described
Pandit	1992	1	Male	69	0	16	Manipulation Other

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Parenti	1999	1	Female	50	1, 3	1, 5, 8, 14, 24, 25, 35, 36	Manipulation Rotation
Parkin	1978	1	Female	23	3, 4, 14	6, 8, 26, 35, 39	Manipulation Rotation
Parwar	2001	1	Female	44	1	7, 9, 14, 35	Manipulation Rotation
Patel	2008	1	Female	29	3	5, 33, 35, 39, 40	Manipulation Not Described
Patel	2008	1	Female	37	3	8, 9, 14, 26, 40	Manipulation Not Described
Peters	1995	1	Female	29	1, 14	32, 34, 35	Manipulation Rotation
Phillips	1989	1	Male	39	3, 4	5, 26, 33	Manipulation Not Described
Povlsen	1987	1	Female	36	11	24, 25, 33, 35, 44	Manipulation Not Described
Powell	1993	1	Male	57	11	26, 35	Manipulation Not Described
Prasad	2006	1	Female	37	10	14	Manipulation Not Described
Preul	2012	1	Female	33	3	3, 14, 26, 39	Manipulation Not Described
Putnam	1986	1	Male	34	15	41	Manipulation Not Described
Quintana	2002	1	Female	32	3	6, 24, 26, 30	Manipulation Rotation
Raskind	1990	2	Female	43	3	3, 6, 8, 14, 24, 26, 30, 32, 36, 39	Manipulation Not Described

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Raskind	1990	2	Male	42	3	8, 35	Manipulation Not Described
Raskind	1990	2	Female	42	3	5, 8, 25, 39	Manipulation Not Described
Raskind	1990	2	Male	32	3	7, 8, 14	Manipulation Not Described
Roberts	1907	1	Male	Unknown	7	3	Manipulation Rotation
Rothrock	1991	1	Male	35	3	4, 6, 8, 24, 25, 26, 30	Manipulation Rotation
Sahathevan	2011	1	Female	33	7, 17	8, 13, 26, 35	Manipulation Rotation
Saint-Elie	2012	1	Male	34	1	8, 9, 14, 26	Manipulation Not Described
Saxler	2004	1	Male	27	13	6, 14, 24, 25	Manipulation Not Described
Schilgen	1997	1	Female	30	3	8, 39,	Manipulation Rotation
Schmidley	1984	1	Male	52	7	8, 26	Manipulation Not Described
Schmitt	1982	1	Male	67	7	9, 10, 13	Manipulation Rotation
Schmitz	2005	1	Female	37	7	0	Manipulation Not Described
Schram	2001	1	Male	41	0	16	Manipulation Rotation
Sedat	2007	1	Female	46	1	6, 7, 14, 20	Manipulation Not Described
Sedat	2007	2	Female	42	1	5, 14, 24	Manipulation Rotation

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Segal	1996	2	Female	33	13	8, 9, 13, 21, 22, 35	Manipulation Not Described
Sherman	1987	1	Male	37	3	1, 6, 24, 25, 32, 33, 35, 39	Manipulation Other
Simnad	1997	1	Female	45	1	7, 9, 14, 35	Manipulation Rotation
Simnad	1997	1	Female	45	5	9, 35, 48	Manipulation Rotation
Sinel	1993	1	Female	32	3, 4	4, 21, 24, 25, 30, 33	Manipulation Rotation
Sternbach	1995	1	Female	32	3	6, 9, 13, 26, 35, 36, 39	Manipulation Not Described
Sturzenegger	1993	1	Male	41	3	5, 9, 33, 40, 47	Manipulation Not Described
Sturzenegger	1993	1	Male	41	3	6, 33	Manipulation Not Described
Suh	2005	1	Female	37	10	9,14	Manipulation Rotation
Talluri	2009	1	Male	41	11	8, 21, 22, 26, 35	Manipulation Not Described
Tazelaar	2014	1	Female	63	10	1, 14, 25, 34	Manipulation Rotation
Terrett	1988	2	Male	42	3	3, 4, 6, 9, 24, 25, 26, 34, 35, 47	Manipulation Not Described
Terrett	1988	2	Female	29	3	4, 8, 9, 26, 35, 47	Manipulation Not Described
Terrett	1988	2	Male	43	3	3, 5, 25, 32	Manipulation Rotation

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Terrett	1988	2	Male	31	14	3, 8, 32, 34,35	Manipulation Not Described
Terrett	1986	2	Male	17	6, 7	9	Manipulation Not Described
Terrett	1986	2	Female	58	6, 7, 17	8, 26, 35	Manipulation Not Described
Terrett	1986	2	Female	21	6, 17	9	Manipulation Not Described
Tinel	2008	1	Female	39	3, 14	3, 35	Manipulation Not Described
Tome	1993	1	Male	54	0	16	Manipulation Not Described
Tomic	2014	1	Male	27	0	12, 14, 26	Mobilization Traction
Tseng	2002	1	Female	67	10	8, 9, 21, 26	Manipulation Not Described
Tseng	2002	1	Male	37	11, 17	21, 26, 35	Manipulation Not Described
Tseng	2002	1	Male	38	11, 17	8, 13	Manipulation Not Described
Van Zagten	1993	1	Male	31	13	8, 21, 22 , 35	Mobilization Traction
Vibert	1993	1	Female	33	3	1, 6, 24, 25, 33 ,35	Manipulation Rotation
Weinstein	1991	1	Male	29	11	5, 8, 9, 20, 25, 26, 33	Manipulation Not Described

Supplemental Table 1. Continued

Author	*Year*	*Type of study*	*Gender*	*Age*	*Type of AE*	*Signs and Symptoms*	*Used Technique*
Wise	2008	1	Female	37	3	14, 24, 25, 26	Manipulation Not Described
Wolff	1989	1	Female	46	11	9, 13	Manipulation Rotation
Wong	2012	1	Female	44	17	8, 26	Manipulation Not Described

Legenda/ Abbreviations:

Type of study

1. Case Report
2. Retrospective Case Series
3. Survey

Type of Adverse Event (AE)

1. Dissection ICA (Internal Carotic Artery) (ICD10-S15.0 / I72.0)
2. Dissection ECA External Carotic Artery) (ICD10-S15.0 / I72.0)
3. Dissection VA (Vertebral Artery) (ICD10-S15.1 / I72.6)
4. Dissection BA (Basilar Artery) (ICD10-I72.5)
5. Dissection intracranial
6. Dislocation ICF-B7150 / ICD10-S13.1)
7. Fracture ICD10-S12
8. Sprain and Strain Cervical Spine (ICD-S13.4)
9. Rupture Muscle or tendon (ICD-S16)
10. Meninges injury
11. Traumatic rupture of Cervical Intervertebral disc (ICD10-S13.0)
12. Spinal cord leasion
13. Spinal cord swelling
14. Trombus
15. Esophagus tear
16. Chiari type 1 Malformation
17. Spinal cord compression
18. Intra-cranial hypotension

Signs and Symptoms

1. Deafness ICD10-H91.9
2. Skin rash ICD10-L98
3. Coma ICF-B110
4. Fainting ICD10-R55
5. Dizziness ICD10-R42
6. Vertigo ICD10-H81.9
7. Visual disturbance ICF-B210
8. Altered sensation ICF-B240
9. Pain ICF-B2801
10. Increased pain during movement ICF-B2801
11. Joint pain ICD-M25.5
12. Muscle tenderness ICD10-M79.1
13. Radiating pain ICF-B2803
14. Headache ICF-28010
15. Migraine ICD10-G43
16. Breathing difficulties ICF-B440
17. Anxiety ICF-B152
18. Panic attack ICD10-F41
19. Depression ICD10-F32
20. Loss of movement ICF-B710
21. Loss or reduced bladder control ICF-B6200
22. Loss or reduced bowel control ICF-B5253
23. Palpitations ICD10-F45.3
24. Vomiting ICD10-R11
25. Nausea ICF-5350
26. Control of voluntary movements ICF-B760
27. Fatigue / Yawn ICD10-R53
28. Flushing ICD10-R23.2
29. Severe sweating ICD10-F45.3
30. Stroke ICD10-I69
31. Transient Ischaemic Attack (TIA) ICD10-G45
32. Death
33. Dysartria
34. Obtundation
35. Paresis
36. Aphasia
37. CSF leakage

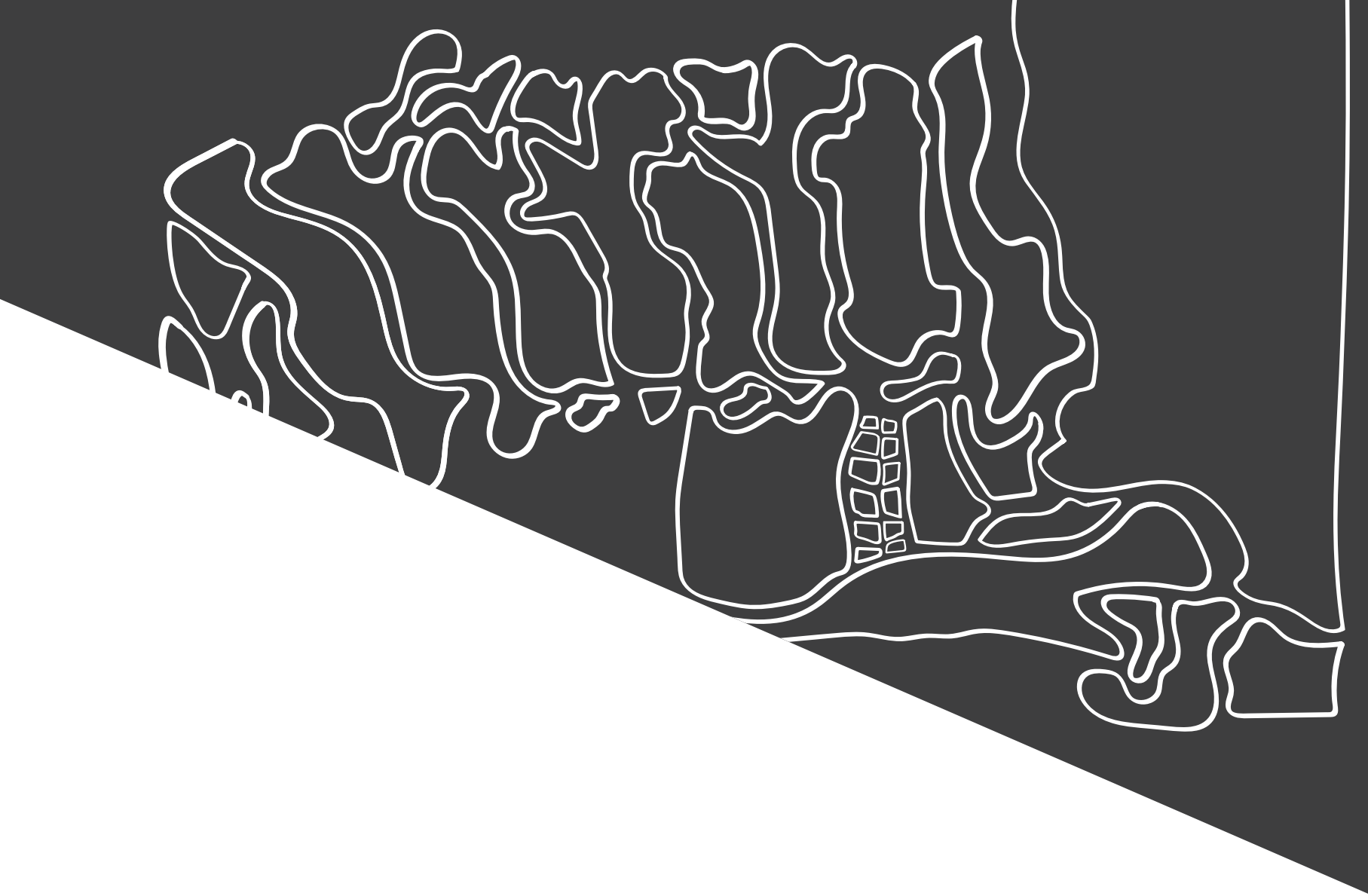
38. Brown-Sequard syndrome
39. Nystagmus
40. Swallowing
41. Swelling
42. Memory loss
43. Neglect
44. Locked-in syndrome
45. Hornes syndrome
46. Dysfagia
47. Wallenberg syndrome
48. Ptosis

APPENDIX 2

SUPPLEMENTAL METHODS: SEARCH STRATEGIES

Search string PUBMED:

("adverse effects"[Subheading] OR "adverse effect"[All Fields] OR "adverse effects"[All Fields] OR "adverse event"[All Fields] OR "adverse events"[All Fields] OR "complications"[MeSH Subheading] OR "complication"[All Fields] OR "complications"[All Fields] OR "Stroke"[Mesh] OR "Stroke"[All Fields] OR "Strokes"[All Fields] OR "Accidents"[Mesh] OR "Accident"[All Fields] OR "Accidents"[All Fields] OR "Blood Vessels"[Mesh] OR "Blood Vessel"[ALL Fields] OR "Blood Vessels"[ALL Fields] OR "Basilar Artery"[All Fields] OR "Basilar"[All Fields] OR "Artery"[All Fields] OR "Arteries"[All Fields] OR "Carotid Arteries"[Mesh] OR "Carotid"[All Fields] OR "Tunica Intima"[Mesh] OR "Tunica Intima"[All Fields] OR "Risk Factors"[Mesh] OR "Risk Factor"[All Fields] OR "Risk Factors"[All Fields] OR "Neck Injuries"[Mesh] OR "Injury"[All Fields] OR "Injuries"[All Fields]) AND ("Neck"[Mesh] OR "Neck"[All Fields] OR "Cervical"[All Fields]) AND ("Musculoskeletal Manipulations"[Mesh] OR "Manipulation"[All Fields] OR "Manipulations"[All Fields] OR "Chiropractic"[Mesh] OR "Chiropractic"[All Fields] OR "Osteopathic Medicine"[Mesh] OR "Osteopathic"[All Fields]) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields] OR "aged"[MeSH Terms] OR "aging"[MeSH Terms] OR "aging"[All Fields] OR "ageing"[All Fields] OR "elderly"[All Fields] OR Elders[All Fields] OR "middle aged"[MeSH Terms] OR "middle aged"[All Fields] OR Senior[All Fields] OR Seniors[All Fields]) AND ("Retrospective Studies"[Mesh] OR "Case Reports"[Publication Type] OR "case report"[All Fields] OR "case reports"[All Fields] OR "retrospective case serie"[All Fields] OR "retrospective case series"[All Fields] OR "retrospective case survey"[All Fields]) NOT (femur[All Fields] OR cervix[All Fields]))



RESPONSE LETTER TO: ADVERSE EVENTS ASSOCIATED WITH THE USE OF CERVICAL SPINE MANIPULATION OR MOBILIZATION AND PATIENT CHARACTERISTICS: A SYSTEMATIC REVIEW

4b

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RESPONSE LETTER TO: ADVERSE EVENTS ASSOCIATED WITH THE USE OF CERVICAL SPINE MANIPULATION OR MOBILIZATION AND PATIENT CHARACTERISTICS: A SYSTEMATIC REVIEW

We wish to thank Dr. Tuchin for his letter to the Editor(Tuchin, 2017) in response to our paper. However, we dispute his contention that our reporting of cervical artery dissection in 57% of reported cases may give the reader "a very distorted picture on risks of dissection". The data speaks for itself. Although cervical arterial dissections (CeAD) is one of the most serious adverse events (AE), in our review we appraised all described AE and not only CeAD. Furthermore, as we described in our discussion, we did not address causality in our review. (Kranenburg et al., 2017)

As we pointed out in our introduction and discussion, major AE seem to be rare and appear to be under-reported. The fact that AE following cervical spine manipulation or mobilization are under-reported makes determination of the exact incidence rates impossible to accurately determine. We agree that the risk is very low when compared to other interventions for neck pain and headaches, but that should not absolve clinicians from considering risks and benefits in the use of cervical spine manipulation. We acknowledge that factors such as a latency periods make it harder to identify and report AE. Due to this delay of symptoms, the manipulating professional might not even be aware of the AE following his/her treatment. Nevertheless, we strongly advise all manipulating professionals to report AE properly with detailed patient characteristics and treatment information. Particularly, since the patient and treatment characteristics in those reports may be of great value to identify patients at risk.

We did not feel the issue of whether published papers mistakenly stated it was a "chiropractic treatment" or a "chiropractic manipulation" was worth commenting on. The aim of our review was to examine the association between serious AE following manipulation and patient characteristics. It was not our intention to cast blame on any one profession for the occurrence of such AE. However, we stand by the accuracy of figure 3 in our paper. In contrast to what Dr. Tuchin seems to suggest, we collected all data from the full-text articles and not from the titles or abstracts. The paper by Hufnagel et al(Hufnagel et al., 1999), describes 10 CeAD cases following 'chiropractic manipulation' performed by 'non-chiropractors'. However, in that paper the professionals were summarized, and it was not clear which professionals were involved in the 10 individual cases. Consequently, we identified all professionals in those cases as "unknown" and assigned them appropriately in figure 3.

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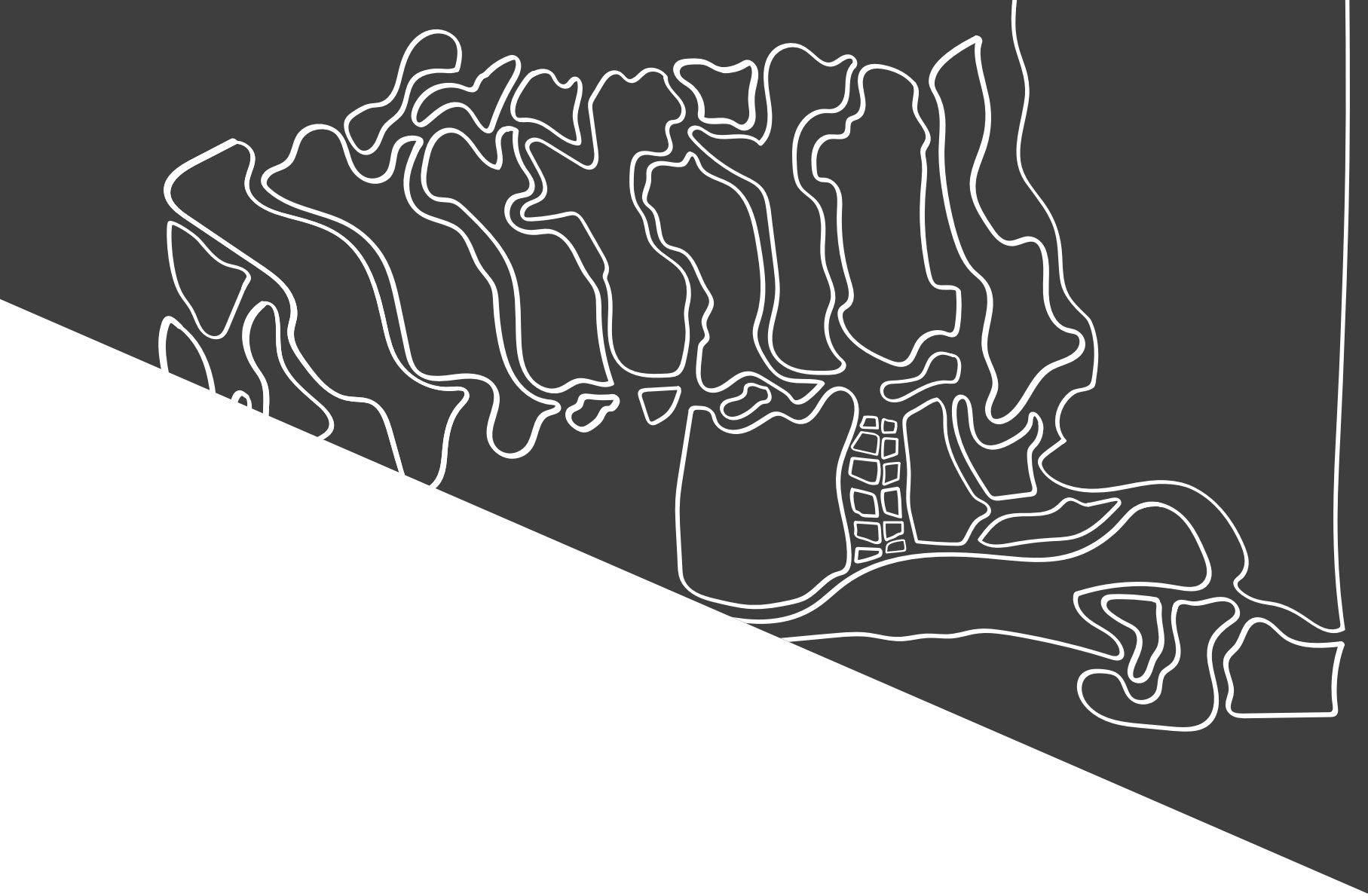

CAROTID AND VERTEBRAL ARTERIAL DISSECTIONS AFTER MANUAL PHYSICAL THERAPY: A CASE CONTROL STUDY

5

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Submitted

ABSTRACT

Introduction: An extra-cranial cervical arterial dissection (CeAD) can present like musculoskeletal neck pain or headache complaints. Therefore, it is important to identify these CeAD patients prior to treatment by manual physical therapists. The first aim of this study is to estimate the proportion of patients with CeAD that received a recent CSM. The second aim is to determine differences in patient demographics and clinical characteristics between patients with CeAD and controls receiving CSM in primary care.

Method: CeAD cases were identified and analyzed from three departments in the University Medical Centre Groningen. A case-control design was used to compare CeAD risk factors based on the IFOMPT framework between CeAD patients with patients receiving cervical manipulations in primary care. Cases and controls were individually matched and Pearson Chi Square and Fishers Exact were used to analyze differences.

Results: Sixty-nine CeAD patients were included in which a CeAD was diagnosed 70 times. The proportion of patients with CeAD that received a CSM prior to hospitalization was low (two) No relevant significant differences were found between patients with CeAD (cases) and neck pain or headache patients without a CeAD receiving a CSM in clinical practice (controls). Most spontaneous CeAD's occurred during summer.

Discussion: These results confirm the difficulty manual physical therapists experience in identifying the sporadic patients with a CeAD in clinical practice. Based on our results, manual physical therapists are advised to use the IFOMPT framework to enhance the clinical reasoning process instead of as a screening tool.

INTRODUCTION

An extra-cranial cervical arterial dissection (CeAD) is a tear in the interior wall of an internal carotid or vertebral artery and is considered to be an important cause of ischemic stroke in young and middle-aged adults.(Debette, 2014) The incidence of carotid CeAD and vertebral CeAD is respectively estimated around 2.6-3.0/100.000 and 1.0/100.000 individuals per year, with a mean age of 45 years.(Blum and Yaghi, 2015; Debette et al., 2009)

One of the early clinical symptoms of CeAD is neck pain or headache.(Debette et al., 2009) The presentation of those dissection-related symptoms are almost similar to the presentation of neck pain or headache symptoms from a musculoskeletal origin. (Debette et al., 2009; Hutting et al., 2018; Thomas, 2016) Generally, in patients with neck pain and headache consulting a manual physical therapist, these complaints have a musculoskeletal origin. For those patients, cervical manipulations (CSM) could be effective to relieve pain and regain function.(Bier et al., 2018; Blanpied et al., 2017; Gross et al., 2015) On the other hand, a CSM could be considered as a minor trauma. Therefore, it might be a potential trigger for a pre-existing CeAD in patients with neck pain from a vascular origin.(Debette et al., 2009; Thomas, 2016) Thus, CSM might induce a CeAD or aggravating a pre-existing dissection in a susceptible patient.(Eriksen et al., 2011) Suggested stroke rates following CSM range from 1/50,000 to 1/6,000,000 CSM.(Assendelft et al., 1996; Magarey et al., 2004; Nielsen et al., 2017) However, these rates seem debatable since conclusive evidence is missing for a causation between CSM and stroke on one hand and an underreporting of cases on the other hand.(Chaibi and Russell, 2019; Church et al., 2016; Hutting et al., 2018; Kranenburg et al., 2017) Notwithstanding, the rarity of CeAD makes solid epidemiological research challenging.

It is essential for manual therapists to know and recognize potential risk factors for CeAD, because of CeAD and its association with CSM. Also, clinical signs and symptoms which might not be of musculoskeletal origin, could be related to a pre-existing CeAD. To assist the manual therapists in this pre-manipulative process, the International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) has developed an international framework.(Rushton et al., 2014) This framework provides guidance for manual physical therapists to construct a patient-centered pre-manipulative risk/benefit analysis, which might reduce the risk of major adverse neurovascular events following CSM. The framework was originally produced as a guidance document and therefore has an informative character. It comprises contraindications, risk factors, precautions, differential diagnoses and specific

tests for a physical assessment. Despite its intended purpose, in clinical practice the framework is regularly used as a screening tool for making clinical decisions. However, risk factors other than those defined in the IFOMPT framework have been described.(Baumgartner et al., 2005; Dabbouseh and Ardelt, 2011; Lee et al., 2006) For example, a seasonal variability of CeAD incidence has been suggested. (Grau et al., 1999; Kloss et al., 2012; Schievink et al., 1998; Thomas et al., 2017) The increase of CeAD seems to be higher in autumn and might be explained by the hypothesis that there is an increase in infections and coughing in autumn.(Kloss et al., 2012; Thomas et al., 2017) Therefore, the IFOMPT framework might be inconclusive.(Hutting et al., 2018) Furthermore, the exact validity and reliability of this framework as a screening tool is currently unknown.

The first aim of this study is to estimate the proportion of patients with CeAD that received a recent CSM. The second aim is to determine differences in patient demographics and clinical characteristics between patients with CeAD and controls receiving CSM in primary care.

METHODS

PARTICIPANTS

Participants were recruited for 1] the dissection group: patients who were hospitalized and had a diagnosed cervical dissection; and 2] the control group: patients who were treated with CSM and did not report any major adverse event afterwards. The dissection group comprised patients who were hospitalized with the indication of cervical dissection and were collected at the University Medical Centre Groningen (UMCG). Controls were recruited in three private practices spread over The Netherlands. All patients receiving a cervical spinal manipulation as a part of their usual treatment were eligible to participate.

MATCHING

To minimize confounding, cases were matched for gender and age (Mansournia et al., 2018), using a range of 5 years for age.

PROTOCOL

DISSECTION GROUP

All medical records from the departments of Neurology, Neurosurgery and the Emergency Room from the UMCG concerning the years 2014, 2015 and 2016 were identified and analyzed. Cases of ischemic or hemorrhagic stroke were used for data collection. Identified cases were retrieved from the hospital information system

and searched for patient demographics, clinical characteristics and (pre-)existing risk factors for CeAD. To increase the quality of the screening, all selected medical records were independently screened by two reviewers.(Waffenschmidt et al., 2019) All records were analyzed by the first reviewer (RK) and all were also independently screened by a second reviewer (ILS, TC or SK) If no agreement could be obtained, a specialized stroke neurologist (GJL) made the final decision. Cases were included if a patient was diagnosed with a dissection of the vertebral artery (VAD, ICD10-S15.1 / I72.6) or the internal carotid artery (ICAD, ICD10-S15.0 / I72.0). Patient files in which an intracranial dissection, basilar artery dissections and cases of subarachnoid hemorrhage were diagnosed were excluded. Furthermore, cases in which a CeAD originated during an invasive procedure were considered a complication of that procedure and were excluded.

CONTROL GROUP

Patients receiving CSM as a part of their treatment as planned who did not experience any major adverse events afterwards were potential participants. Patients were excluded if they had previously experienced a CeAD.

OUTCOME MEASURES

The number of patients hospitalized with a CeAD and the season in which their CeAD occurred was inventoried. Furthermore, patient characteristics (gender and age), the CeAD risk factors as described in the IFOMPT framework section 3.2 were inventoried.(Rushton et al., 2014) These factors were supplemented with: 1] alcohol abuse; 2] cocaine abuse; 3] familiar cardiovascular history; 4] oral anticonception; and 5] vascular trauma.(Biller et al., 2014; Dabbouseh and Ardelt, 2011) If a variable was not present in the patient file, it was scored as “Absent/ Unknown”. For the control group, the same patient demographics, risk factors and precautions for CeAD as in the dissection group were collected.

ETHICS

This study was registered in the UMCG Research Register (RR201500994) and the medical ethical committee of the UMCG approved a waiver (METc 2015/465) for this study.

DATA ANALYSIS

All analyses were performed using IBM SPSS statistics 23. Descriptive statistics were used to characterize the data sampled from each of the groups. All data was presented in frequencies and percentages unless otherwise noted. For the

comparison of risk factors between the two groups a Pearson Chi Square or a Fishers Exact was used on the corresponding contingency tables. When the observed or the expected count was <10 the Fishers Exact was used. Significance was set at level $\alpha < 0.05$. Hypertension was not tested for difference during the case-control comparison. Since blood pressure was measured after the CeAD event, instead of before, an unobtrusive comparison was unfortunately not possible.

RESULTS

PARTICIPANTS

Of the 1,687 identified patients hospitalized with a stroke, a dissection was diagnosed 70 times (4.1%) in 69 patients. In 31 patients the dissection originated in the vertebral artery (44%) and in 39 the dissection originated in the internal carotid artery (56%). Furthermore, in four cases of VAD and one case of ICAD the arteries were bilaterally affected. The mean (sd) age at onset was 54 (15) years and 46 (66%) of 70 patients were male. Of the CeAD, 13 cases occurred during spring, 23 cases in the summer, 17 cases in the autumn and 13 cases in the winter. Two patients (3%) described recent CSM in the medical record. Unfortunately, no details were described if the CSM was considered the cause of the CeAD, regarding the CSM provider, the used technique, the time between the applied CSM and hospitalization. The ages of the CSM cases at onset were 22 and 48 and the male/female ratio was distributed evenly. The early clinical characteristics of the CSM cases were cervical pain (50%), headache (50%), ptosis (50%) and an asymmetry of the mouth/ tongue (100%). The late clinical characteristics were CVA (100%), Wallenberg syndrome (50%), diplopia (100%), dizziness (100%), nystagmus (50%), numbness (100%), nausea (50%) and ataxia (100%).

In the control group 168 patients who received a CSM in a private practice were included. They had a mean age of 47.7 years (SD18) and 110 were females (65.5%).

MATCHING

Of the dissection patients, 66 could be matched 1:1 to a control. The hindering parameter for the remaining three males were their high ages (85, 87 and 90 years). There were no patients who received cervical manipulations within their age range. Therefore, these cases were excluded from the comparison of the two groups.

COMPARISON

Two risk factors ‘neck or head trauma’ and ‘long term steroid use’ as described in the IFOMPT framework (Rushton et al., 2014, sec. 3.2) were found to be significantly

different between the cases and the controls. However, the significance was due to a larger presence in the control group.

Table 1. The presence of CeAD risk factors in hospitalized CeAD patients and controls (n=66 in each group), accompanied by results of the Chi Square or Fishers Exact.

		Case	Control	P-value	
# Anticoagulation disorder	No	100%	95%	.244	
	Yes	0%	5%		
# Cardiovascular history	No	67%	80%	.114	
	Yes	33%	20%		
# Diabetes Mellitus	No	89%	97%	.164	
	Yes	11%	3%		
# Hypercholestemia/ hyperlipidemia	No	79%	80%	1.000	
	Yes	21%	20%		
# Migraine	No	91%	95%	.492	
	Yes	9%	5%		
# Neck or Head trauma	No	97%	80%	.002	*
	Yes	3%	20%		
# Hyperhomocystenia	No	100%	100%	NC	
	Yes	0%	0%		
# Long term steroid use	No	100%	91%	.028	*
	Yes	0%	9%		
# Postpartum (lactation period)	No	100%	98%	.394	
	Yes	0%	2%		
# Recent cervical manipulation	No	97%	94%	.274	
	Yes	3%	6%		
# Recent infection	No	100%	94%	.119	
	Yes	0%	6%		
# Smoking	No	74%	80%	.534	
	Yes	26%	20%		
Alcohol abuses	No	97%	97%	1.000	
	Yes	3%	3%		
Cocaine use	No	100%	98%	1.000	
	Yes	0%	2%		
Familiar Cardiovascular history	No	77%	70%	.431	
	Yes	23%	30%		

Table 1. Continued

		Case	Control	P-value
Oral anticonception	No	97%	93%	.381
	Yes	3%	7%	
Vascular trauma	No	100%	98%	1.000
	Yes	0%	2%	

NC = Not computed; # = IFOMPT framework risk factor (§3.2); * = P≤ 0.05

DISCUSSION

The proportion of patients with CeAD that received a CSM prior to hospitalization was low (two out of 69) in our sample. Furthermore, all IFOMPT risk factors were absent in the majority of our sample (Table 1).(Rushton et al., 2014, sec. 3.2) The comparison between the cases of the hospitalized patients with CeAD and the patients receiving CSM in primary care did not confirm relevant risk factors in patients receiving CSM. Although 'neck and head trauma' resulted in a significant difference between the two cases and the controls, this was due to the larger presence in the controls. The latter might well be explained by the phenomenon that people experience neck pain or headache after their neck or head trauma and seek help from a manual physical therapist to relieve their pain or to improve their cervical function. Other risk factors also demonstrated no significant differences between the cases and the controls. (Table 1)

In two patient files out of 69 for patients with CeAD a CSM was described in the patient history. However, in both cases the CSM was described as any other usual risk factor and an expected causal relation between the CSM and the CeAD was not mentioned at all. Consequently, this suggests that none of the CeAD's was caused by a CSM. It might be that those two patients sought help for neck pain due to an underlaying CeAD. The typical stuttering start of the CeAD with vague symptoms could be an explanation for these treatments. However, it might be more likely that those 2 patients sought help for an autonomous episode of musculoskeletal neck pain which occurred before the start of the CeAD. In contrast to the low estimated incidence of CeAD, the incidence of neck pain in The Netherlands is estimated at 16%.(Kim et al., 2018) Additionally, neck pain is seldom caused by serious pathology. (Blanpied et al., 2017)

In our samples, there seem to be no relevant differences between the cases and the controls. Therefore, our data seems to suggest that the risk factors for CeAD

as described in section 3.2 of the IFOMPT statement might not be suitable for use as a CeAD screening instrument. (Rushton et al., 2014) The intention of the IFOMPT framework was to enhance the clinical reasoning process and has an informative character. However, in clinical practice it is also regularly interpreted as a screening tool or seen as guideline to assist during a medico-legal case.(Thomas et al., 2019) The IFOMPT framework was not developed with that intention since the evidence at the time was limited and inadequate. Currently, evidence is still limited and will probably remain challenging since the clinical signs of spontaneous CeAD are only present in fewer than one-third of the patients.(Chaibi and Russell, 2019; Thanvi et al., 2005; Thomas, 2016)

In our sample most of the patients with CeAD were hospitalized during the summer. This seems to contrast with other literature discussing seasonality.(Grau et al., 1999; Kloss et al., 2012; Schievink et al., 1998; Thomas et al., 2017) Seasonality might be seen as an external or environmental factor leading to CeAD.(Baumgartner et al., 2005, pp. 44–53) Several theories have been proposed to explain the seasonality of CeAD occurrence, including weather related changes in blood pressure, coagulation parameters, diet and infections. (Baumgartner et al., 2005, pp. 44–53) The hypothesis that the presence of (upper-respiratory) infections is higher during the cold seasons and minor traumata like sneezing and coughing would be the triggering factor could not be confirmed by a large cohort study including 960 patients with CeAD.(Kloss et al., 2012)

LIMITATIONS

Our sample of patients hospitalized with CeAD were included from a comprehensive stroke center. The patients referred to these specialized centers are usually younger or have more complicated or serious symptoms. Therefore, selection bias might have played a role in the data collection. Furthermore, since the cases were retrospectively analyzed, it is uncertain whether all relevant information has been obtained and subsequently recorded in the patient file. Some risk factors like genetic factors or CSM are rare and might not have been checked or tested. Additionally, the low number (n=2) of patients with a CeAD and a CSM described in their file made it unfeasible to use these as a separate group for comparison.

STRENGHTS

Our sample comprised a substantial number (n=70) of CeAD patients from which a complete patient file was analyzed independently by two researchers. To improve the quality, the first researcher analyzed all patient files. Three other researchers

each also analyzed one third of the patient files. These four researchers were all manual physical therapists with advanced training and were all familiar with the IFOMPT framework.(Rushton et al., 2014) A specialized stroke neurologist (GJL) was consulted in three cases to obtain consensus.

FUTURE RESEARCH

A case-control study using a larger sample and three groups: 1] patients with CeAD; 2] patients with CeAD who experiences a recent CSM; and 3] a control group of patients without a CeAD experiencing a CSM might bring other relevant factors to the table. If international groups of cases were to be combined, the larger sample and intercultural differences would strengthen the study.

CONCLUSIONS

Few (n=2) cases of patients with CeAD who experienced a CSM were identified amongst 69 patients with a CeAD. Furthermore, no relevant significant differences were found between patients with CeAD and neck pain or headache patients without a CeAD receiving a CSM in clinical practice. These results confirm the difficulty manual physical therapists experience in identifying the sporadic patients with a CeAD in clinical practice. Based on our results, manual physical therapists are advised to use the IFOMPT framework to enhance the clinical reasoning process instead of as a screening tool.

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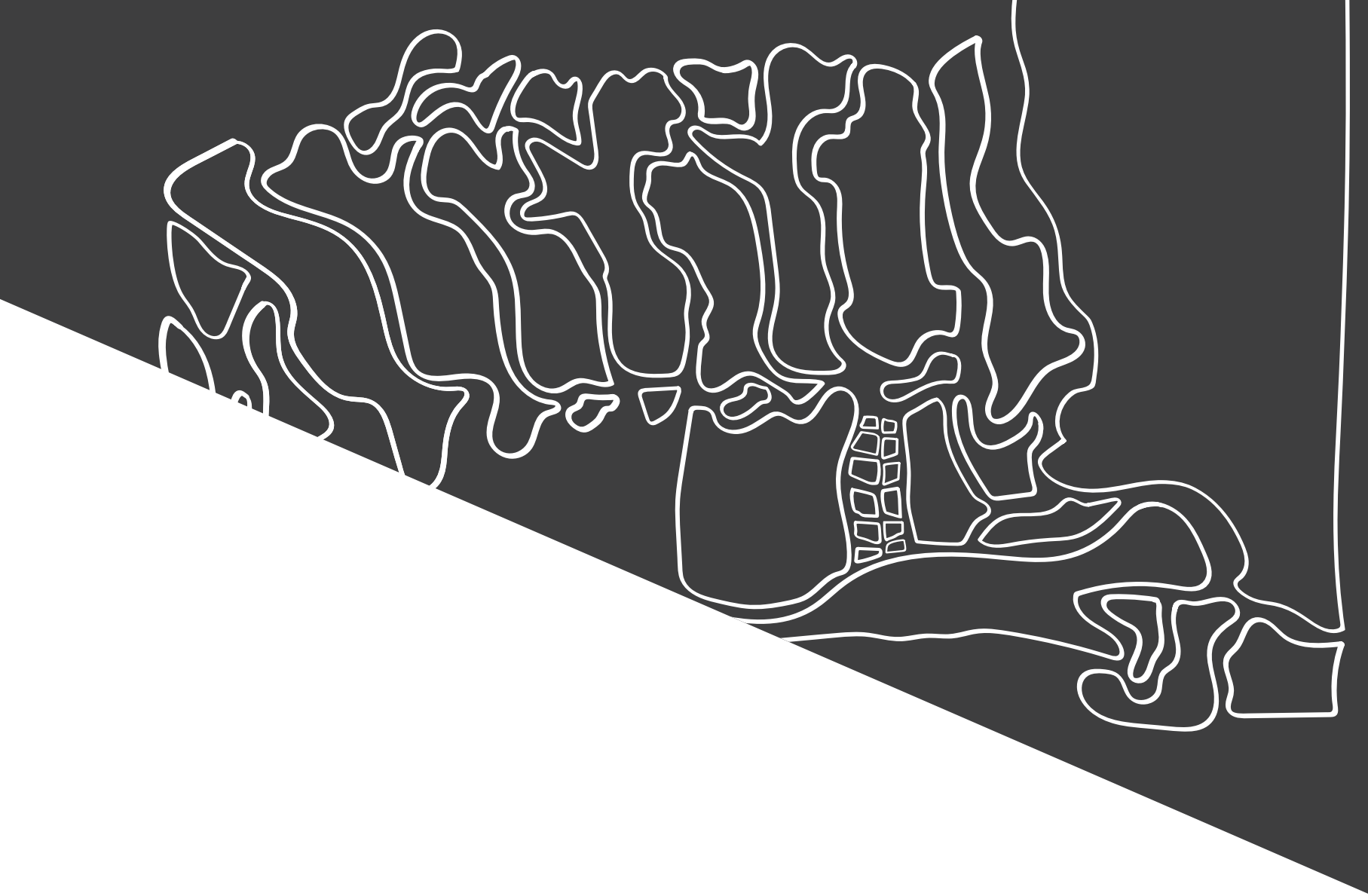

EFFECTS OF HEAD AND NECK POSITIONS ON BLOOD FLOW IN THE VERTEBRAL, INTERNAL CAROTID AND INTRACRANIAL ARTERIES: A SYSTEMATIC REVIEW

6

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ABSTRACT

Background: Manual therapy interventions targeting the neck comprise various positions and movements of the cranio-cervical region. The hemodynamic changes in various spinal positions potentially have clinical relevance.

Objectives: To investigate the effects of cranio-cervical positions and movements on hemodynamic parameters (blood flow velocity and/or volume) of cervical and cranio-cervical arteries.

Methods: Four databases were searched (Pubmed, Embase, CINAHL and ICL). Subsequently, a hand search of reference lists was performed, and experts were consulted. Full text experimental and quasi-experimental studies on influence of cervical positions to blood-flow of the vertebral, the internal carotid and the basilar artery were eligible for this review. Two independent reviewers selected and extracted the data using the double screening method.

Results: Of the 1453 identified studies 31 studies were included and comprised data on 2254 participants. Most studies mentioned no significant hemodynamic changes during maximal rotation (n=16). A significant decrease in hemodynamics was identified for the vertebral artery with a hemodynamic decrease in the position of maximum rotation (n=8) and combined movement of maximum extension and maximum rotation (n=4). A similar pattern of decreased hemodynamics was also identified for the internal carotid and intracranial arteries. Three studies focused on high velocity thrust positioning and movement, all reported no hemodynamic changes

The synthesized data suggest that in the majority of people most positions and movements of the cranio-cervical region do not have an effect on blood flow.

Conclusions: The findings of this systematic review suggest that cranio-cervical positioning may not alter blood flow as much as previously expected.
Level of Evidence: 2a

INTRODUCTION

Manual therapy interventions for the management of people with head and neck pain are performed utilising various positions and movements of the cranio-cervical region. These interventions have rarely been associated with adverse events. (Kranenburg et al., 2017; Nielsen et al., 2017) Exact incidence rates of adverse events are unknown and causality between intervention and adverse events is debated. (Church et al., 2016; Nielsen et al., 2017) Variables such as specific techniques, screening tests, and patients' characteristics have been studied in an attempt to enhance the safety of treatment. Unfortunately, studies have been unable to identify specific variables which relates to the increase or mediation of risk for adverse events.(Haldeman et al., 1999; N. Hutting et al., 2013; Nathan Hutting et al., 2013; Kranenburg et al., 2017) However, suspicion remains high that high velocity thrust (HVT) techniques may be associated with adverse events.(Beeton et al., 2010; Wand et al., 2011)

Understanding the clinical relevance of arterial pathologies is essential for health care professionals working with the cervical spine.(Rushton et al., 2014) The broad range of pathologies relevant to clinical reasoning and selecting appropriate interventions are considered under the umbrella term *Cervical Arterial Dysfunction* (CAD).(Kerry et al., 2008) This includes arterial events ranging from atherosclerotic disease to mechanical trauma of vessels. One of the most frequently described adverse events following cervical treatment techniques is arterial dissection. (Kranenburg et al., 2017) Although many other pathological processes are of concern, dissection serves as a useful model to understand the relationship between cervical movement and arterial pathology. The pathophysiology of a dissection is not completely clear. A dissection is characterised by separation of the inner layer (tunica intima) from the middle and outer layers of arterial wall due to mechanical stress. This separation can lead to a partial or full occlusion of an artery and obstruct the blood flow to the brain. Occlusion of one artery may not result in direct brain perfusion problems because of the bilateral supply to the brain. In both dissection and non-dissection events, a semisolid coagulated mass of red and white blood cells can be formed (embolus), eventually as a consequence leading to a critical arterial blockage, resulting in a stroke.(Biller et al., 2014; Debette, 2014)

Several movements of the cervical spine have been postulated to alter the amount of blood flow volume or velocity (hemodynamics) in the cervical vessels.(Mitchell, 2009) For example, cervical end range rotation has been reported to be associated with an increased stress at the walls of the vertebral artery and internal carotid

artery.(Mitchell, 2009) The hemodynamic parameters of blood flow volume and velocity are considered as robust proxy measures of mechanical stress on vessels and are commonly used to investigate mechanical stress on arteries.(Peng et al., 2017) Movement-induced stress could potentially initiate acute pathologies such as dissection, or embolus formation in atherosclerotic pathologies. Due to the unique anatomy of the upper cervical spine, roughly half of cervical rotation occurs at the atlanto-occipital joint. The potential mechanical stress on cervical arteries, occurring during rotation of the upper cervical spine could potentially compromise the arterial wall of a CAD event in progress.(Thomas, 2016) It seems unlikely that a healthy artery would be traumatised by a therapeutic intervention alone.(Thomas, 2016) However, an increase of force (such as a cervical manipulation, mobilisation, or repeated active movement) during naturally occurring arterial stresses might act as either a causative or exacerbating factor leading to a central neuro-vascular event (e.g. stroke).(Debette et al., 2009; Dittrich et al., 2007)

A commonly described symptom of CAD pathologies is neck or head pain, for which patients may seek assistance from a manipulative therapist for evaluation and treatment for relief of pain and improvement of function. Therefore, it is plausible that a CAD is not an adverse event of the treatment itself, but exists *in situ* prior to treatment.(Biller et al., 2014) Understanding mechanical stress each cervical position or movement puts on the cervical arterial arteries could potentially enhance diagnostic reasoning, and the safety of cervical therapeutic interventions. (Biller et al., 2014)

It is hypothesised that mechanical stress on cervical arteries during cervical mobilisation or cervical manipulative techniques can cause CAD, especially in patients with pre-existent vascular pathologies.(Debette et al., 2015; Hartkamp et al., 2018) Insight in mechanical factors (such as cervical artery blood flow during positions and movements of the cervical spine) can potentially help to decrease the risk for the occurrence of CAD after cervical spinal mobilisation or manipulation. Therefore, the aim of this systematic review was to collect and analyze data regarding the effects of cervico-cranial positions and movements on hemodynamic parameters (blood flow velocity and/or volume) of the cervical and cranio-cervical arteries.

METHODS

LITERATURE SEARCH

A systematic search was performed in Pubmed, Embase, CINAHL (Cumulative Index to Nursing and Allied Health) and ICL (Index Chiropractic Literature) in August 2018. No date range was set. The search strategies developed by two authors (HAK and NH) were reviewed and adjusted for each database by a senior librarian. All individual search strategies are provided in appendix 2. Subsequently, additional literature was identified by related articles (PubMed function), hand searching reference lists of articles included in the review.("PubMed," n.d.) Additionally, three experts who published multiple studies on this topic were asked if they felt we missed relevant studies. A grey literature search was not performed.

STUDY SELECTION

The following inclusion criteria were set a priori; 1] experimental and quasi-experimental research on the influence of cervical positions to blood-flow of the vertebral, the basilar and the internal carotid artery; 2] values of the blood flow velocity or blood flow volume were described in neutral and altered cervical position, 3] assessed adult participants, and 4] were published in the English language.

IDENTIFICATION

To identify eligible studies, the 'double screening' method was used.(Shemilt et al., 2016) First, all retrieved records were uploaded to 'Refworks' and de-duplicated. ("Refworks," n.d.) Next, the first and second author (HAK and RT) individually determined the eligibility of the articles. However, to facilitate interrater reliability, results were discussed after each of the first five articles potentially eligible. Articles could be scored as 'included', 'provisionally included', 'excluded' or 'incomplete'. Articles were scored incomplete when titles were incomplete, or abstracts were missing. Differences were discussed and in the case of disagreement the study was included for the full-text analyses. A similar procedure was repeated for the full-text articles. At first, disagreements were discussed, however when no consensus was reached a third author was asked to determine if the study would be included. In circumstances where article did not provide adequate information to determine if the study was eligible, authors of the article were contacted via email.

QUALITY ASSESSMENT.

Since no tool exits to appraise the quality or bias of observational studies or studies for which a reference test does not exist, a modified tool was developed. The foundations of the tool were based on the *Cochrane Handbook for Systematic Reviews*

of Interventions, the '*Quality Assessment of Diagnostic Accuracy Studies – 2*' (QUADAS-2) and the '*Consensus-based Standards for the selection of health Measurement Instruments*' (COSMIN) and the '*Assessing the Methodological Quality of systematic Reviews'* (AMSTAR).(Higgins et al., 2011; Katikireddi et al., 2015; Shea et al., 2009; Whiting et al., 2011) With this tool we critically appraised the selection bias, attrition bias, reporting bias and other bias.(Higgins et al., 2011) The tool consisted of 7 parts: 1] Specific objectives or hypotheses (*Other Bias*); 2] Eligibility criteria for participants (*Selection Bias*); 3] Sample size (*Other Bias*); 4] Detailed description of interventions for each group (*Other Bias*)'; 5] Test conditions similar for all measurements (*Other Bias*); 6] Pre-specified primary and secondary outcome measures (*Attrition Bias*); and 7] All of the predefined outcomes were specified in the results section (*Reporting Bias*). The COSMIN was used for the methodology to weight the sample size (item 3). Two authors with clinical and content specific expertise (HAK) and (MS) appraised all articles individually.(Grindem et al., 2018) At first, disagreements were discussed, however when no consensus was reached a third author was asked to determine the final methodological score.

DATA SYNTHESIS & SUBGROUP ANALYSES

A data extraction sheet was composed based on participant characteristics (for example, age and pathologies), the intervention itself (for instance, test position, cervical position, cervical artery and device) and the effect on blood flow (pre-, during and post intervention blood velocity or blood volume). Collected data were analysed using descriptive techniques.

Subgroup analyses were set a priori and made between; 1] healthy patients versus patients with vascular pathologies and other pathologies; 2] different positions of the cervical spine; and 3] a comparison between neutral position and treatment positions.

RESULTS

The results of the search are presented in Figure 1, PRISMA flowchart. Of the 1453 identified studies 67 were considered potentially relevant and reviewed in full-text, and all disagreements were resolved by consensus. Of the remaining articles, most articles were excluded due to language restrictions. Finally, 31 articles met the inclusion criteria and were analysed by HAK and RT. Results were compared and discussed without the necessity for a third reviewer.

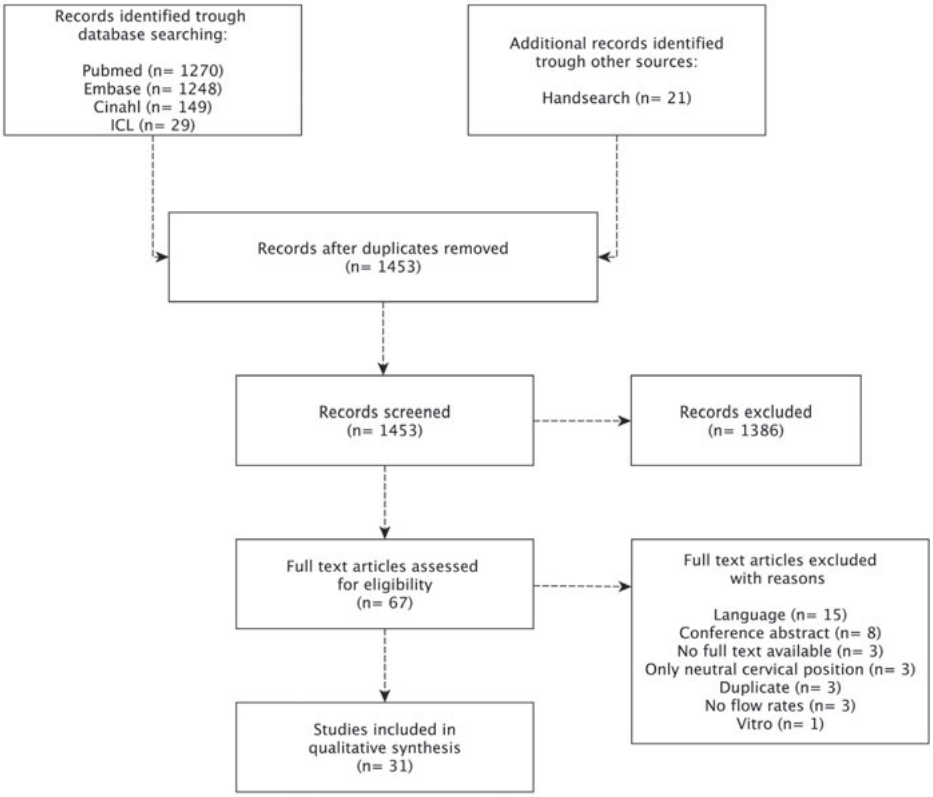

Figure 1. PRISMA flowchart; Selection process of relevant studies

STUDY CHARACTERISTICS

Characteristics of the included studies are summarised in Table 1.

Table 1. Study characteristics

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Hedera et al., 1993)	BA, ACA, MCA, PCA	P1, transtemporal, suboccipital	Neutral, Rotation max, Extension max + rotation max,	41 healthy participants with asymmetry of VA <75%,	=	Me 47.9	Sitting	CDS
				23 males, 18 females		± 14.1		
						R ?		
				11 healthy participants with asymmetry of VA >75%	-	Me 47.3		
				7 males, 4 females		± 13.8		
						R ?		
(Sturzenegger et al., 1994)	BA	P1	Neutral, Rotation max, Extension max, Flexion max,	14 patients with suspected VBI,	=	Me 57	?	CDS
				6 males, 8 females	-	± ?		
						R 34-76		
(Thiel et al., 1994)	VA	C3-5	Neutral, Rotation max, Rotation 5o-15o, Extension max, Extension max + rotation max,	30 healthy participants,	=	Me 28.3	Supine	CDS
				17 males, 13 females		± 5.3		
						R 19-40		
				12 chiropractic patients with a positive Wallenberg,	=	Me 47.4		
				3 males, 9 females	-	± 14.4		
						R 25-68		

Table 1. Continued

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Weintraub and Khoury, 1995)	VA, CA, BA	NA	Neutral, Rotation max, Extension max,	64 patients with suspected ischaemic cerebrovascular disease,	=	Me 70.9	Supine	MRI
				20 males, 44 females	-	± ?		
						R 21-97		
				30 healthy patients,	=	Me 66.3		
				10 males 10, 20 females	-	± ?		
						R 22-80		
(Côté et al., 1996)	VA	C3-C5	Neutral, Extension max + rotation max,	30 healthy participants,	=	Me 28.3	Supine	CDS
				17 males, 13 females		± 5.3		
						R ?		
				12 patients with a positive Wallenberg and dizziness,	=	Me 47.4		
				3 males, 9 females	-	± 14.4		
						R ?		

Table 1. Continued

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Petersen et al., 1996)	BA	C0-C1, suboccipital window	Neutral, Rotation max,	46 patients with VBI	-	Me 62	?	CDS
				28 males, 18 females		± 1.5		
						R 41-83		
				25 healthy young participants,	=	Me 26		
				? males, ? females		± 0.48		
						R 22-30		
				15 healthy elderly participants,	-	Me 59		
				? males, ? females		± 2.06		
						R 50-75		
(Licht et al., 1999)	VA	Origin & Foramen C6	Neutral, Rotation max, Rotation 45o,	20 healthy participants,	=	?	Supine	CDS
				? males, ? females		?		
						?		
(Rivett et al., 1999)	VA, CA	C3-C5	Neutral, Rotation max, Rotation 45o, Extension max + rotation max,	10 patients with a positive premanipulative test,	=	Me 37.9	Supine	CDS
				2 males, 8 females	-	± 13		
						R 24-65		
				10 healthy participants,	=	Me 32.7		
				2 males, 8 females	-	± 10.3		
						R 20-47		

Table 1. Continued

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Yi-Kai et al., 1999)	VA	C0-C1	Neutral, Rotation max, Extension max, Extension max + rotation max,	27 healthy elderly participants,	=	Me 62	?	CDS
				21 males, 6 females		± ?		
						R 60-72		
				23 healthy participants,	=	Me 21		
				23 males, 0 females		± ?		
						R 19-22		
(Licht et al., 2000)	VA	Origin & Foramen C6	Neutral,	20 chiropractic patients with positive vascular premanipulative tests,	=	Med 44	Supine	CDS
			Rotation max,	5 males, 15 females.		± ?		
			Rotation 45o,			R 27-74		
			Extension max + rotation max,					
			Extension max + rotation max + distraction,					
(Haynes and Milne, 2001)	VA	C2	Neutral, Rotation max, Rotation 45o,	20 patients, neck related symptoms,	=	Me 39	Sitting	CDS
				9 males /11 females.		± 4.2		
						R 20-52		

Table 1. Continued

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Haynes et al., 2002)	VA	NA	Neutral, Rotation max,	8 healthy participants, 6 males, 2 females	=	Me 44.4 ± 14.1 R 25-61	Supine	MRA
(Licht et al., 2002)	CA	?	Neutral, Extension max + rotation max,	11 patients with a positive vascular premanipulative test, ? males, ? females	=	Me? ± ? R ?	Supine	CDS
(Mitchell, 2003)	VA	C0-C1	Neutral, Rotation max,	120 healthy participants, 60 males, 60 females	-	Me ? ± R 20-30	Prone	CDS
(Rivett et al., 2003)	VA	C1-2, C2-3	Neutral, Rotation max, Extension max,	20 healthy participants, 8 males, 12 females	=	Me 35.5 ± 9.3 R 24-55	Supine	CDS
(Sakaguchi et al., 2003)	VA	C4-6	Neutral, Rotation max,	1108 patients referred for neurovascular examination, males 710, females 398	-	Me 61.4 ± 12.9 R ?	?	CDS

Table 1. Continued

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Zaina et al., 2003)	VA	C1-2 & C5-6	Neutral, Rotation max, Rotation 45o,	20 healthy participants,	=	Me 32.7	Sitting	CDS
				? males, ? females	-	± 8.82		
						R ?		
(Arnold et al., 2004)	VA	C3-5	Neutral, Rotation max, Extension max,	22 healthy participants,	=	Me 35	Supine	CDS
			Extension max + rotation max,	8 males, 14 females.	-	± 10.5		
			Pre-manip. position,			R ?		
(Mitchell et al., 2004)	VA	C0-C1	Neutral, Rotation max,	30 healthy participants,	=	Me 21	Sitting	CDS
				males 0, females 30	-	± ?		
						R ?		

Table 1. Continued

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Ozdemir, 2005)	VA	C2-C6	Neutral, Rotation max, Rotation 30o,	28 patients with cervical degenerative changes,	=	Me 51	Sitting	CDS
				11 males, 17 females	-	± ?		
						R 44-76		
				24 patients with clinically proven VBI,	=	Me 47		
				14 males, 10 females	-	± ?		
						R 36-58		
				20 healthy participants,	=	Me 36		
				8 males, 12 females	-	± ?		
						R 19-40		
(Sultan et al., 2009)	VA, MCA, PCA	Above C6, P1 & P2	Rotation max,	46 patients with suspected positional VBI,	=	Me 69	Sitting	CDS
			Extension max + rotation max,	16 males, 30 females		± ?		
			Flexion max + rotation max,			R 32-98		
(Bowler et al., 2011)	VA	C2-3,	Neutral, Pre-manip. position,	14 healthy participant	=	Me 31	Supine	CDS
	CA	2cm proximal to bifurcation		3 males, 11 females	-	± 10,76		
						R 19-49		

Table 1. Continued

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Thomas et al., 2013)	VA, CA, TCI	NA	Neutral, Rotation max, Rotation max + distraction, Rotation C1-C2 max, Distraction,	20 healthy participants, 10 males, 10 females	=	Me 33.1 ± 11.9 R 21-59	Supine	MRA
(Quesnele et al., 2014)	VA	C1-C2	Neutral, Rotation max, Rotation 45o, Manip C1-2,	10 healthy participants, 10 males	=	Me 26.8 ± 1.6 R 24-30	Supine	MRI
(Erhardt et al., 2015)	VA	V3	Neutral, Pre-manip. position, Manip C1-2,	23 healthy participants, 9 males, 14 females	=	Me 40 ± ? R 27-69	Supine	CDS
(Thomas et al., 2015)	VA, CA	NA	Neutral, Rotation max,	20 healthy participants, 10 males, 10 females	= -	Me 33.1 ± 11.9 R 21-59	Supine	MRA
(Siwach et al., 2016)	ACA, MCA, PCA	?	Neutral, Extension max, Flexion max,	50 spondylosis patients 23 males, 27 females	=	Me 45.4 ± 11.9 R 20-70	?	CDS

Table 1. Continued

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Saracoglu et al., 2016)	CA	2cm proximal to bifurcation	Neutral, Semi Fowler Extension + 10o collateral rotation	28 patients during thyroid surgery	+	Me 39.1	Supine	CDS
				6 males, 22 females	=	± 9.8		
					-	R 18-50		
(Araz Server et al., 2017)	VA	V1,V2,V3,V4	Neutral, Rotation max, Extension max + rotation 45o,	21 patients with vestibular symptoms,	=	Me 45.5	Supine	CDS
				3 males, 18 females	-	± 11.1		
						R ?		
				21 healthy participants,	=	Me 41.3		
				5 males, 16 females		± 9.2		
						R ?		
(Creighton et al., 2017)	VA	C6 transverse foramen	Neutral, traction	30 individuals (healthy or patients unclear)	=	Me 36.6	Sitting	CDS
				? males, ? females		± ?		
						R 21-57		

Table 1. Continued

Author(s) & year	*Artery*	*Section*	*Cervical positions*	*Population and Gender*	*Hemo-dynamic effect*	*Age*	*Test position*	*Device*
(Niewiadomski et al., 2017)	VA	?	Neutral, rotation 60o	50 patients vertigo a/o hearing loss & vessel anomality	=	Me 49,9	?	CDS
				20 males, 30 females		± ?		
						R 17-79		
				50 healthy participants	=	Me 44.4		
				26 males, 24 females		± ?		
						R 20-71		

Abbreviations: VA: Vertebral Artery, BA: Basilar Artery, ACA: Anterior Cerebral Artery, MCA: Middle Cerebral Artery, PCA: Posterior Cerebral Artery, TCI: Total Cerebral Input, CDS: Colour Duplex Sonography, Me: Mean, Med: Median, ± : SD, R: Range, - : Significant decrease, = : No significant change, + : Significant increase

PARTICIPANTS

The 31 studies comprised data on 2254 patients of which 1162 were male. However, in four studies, with a total of 91 individuals, no gender was specified.(Licht et al., 2002, 1999; Petersen et al., 1996; Zaina et al., 2003) Overall, the mean age of participants was reported in 25 studies and was 55 years ranging from 18 – 98 years.

MEASUREMENTS

The majority (n=26)(Araz Server et al., 2018; Arnold et al., 2004; Bowler et al., 2011; Côté et al., 1996; Creighton et al., 2017; Erhardt et al., 2015; Haynes and Milne, 2001; Hedera et al., 1993; Licht et al., 1999, 2002, 2000; Mitchell et al., 2004; Mitchell, 2003; Niewiadomski et al., 2017; Ozdemir, 2005; Petersen et al., 1996; Rivett et al., 2003, 1999; Sakaguchi et al., 2003; Saracoglu et al., 2016; Siwach et al., 2016; Sturzenegger et al., 1994; Sultan et al., 2009; Thiel et al., 1994; Yi-Kai et al., 1999; Zaina et al., 2003) of the 31 included studies used a Colour Doppler Sonography device to measure flow velocities and flow volumes. The remaining five studies used Magnetic Resonance Angiography (n=3)(Haynes et al., 2002; Thomas et al., 2015, 2013) and Magnetic Resonance Imaging (n=2)(Quesnele et al., 2014; Weintraub and Khoury, 1995).

Participants were mostly tested in a supine position (n=12).(Araz Server et al., 2018; Arnold et al., 2004; Bowler et al., 2011; Côté et al., 1996; Erhardt et al., 2015; Haynes et al., 2002; Licht et al., 2002, 2000, 1999; Quesnele et al., 2014; Rivett et al., 2003, 1999; Saracoglu et al., 2016; Thiel et al., 1994; Thomas et al., 2015, 2013; Weintraub and Khoury, 1995) Other test positions included: sitting (n=7)(Creighton et al., 2017; Haynes and Milne, 2001; Hedera et al., 1993; Mitchell et al., 2004; Ozdemir, 2005; Sultan et al., 2009; Zaina et al., 2003), prone (n=1)(Mitchell, 2003) or were not mentioned (n=6)(Niewiadomski et al., 2017; Petersen et al., 1996; Sakaguchi et al., 2003; Siwach et al., 2016; Sturzenegger et al., 1994; Yi-Kai et al., 1999).

For the vertebral artery, maximum rotation (n=18)(Arnold et al., 2004; Haynes et al., 2002; Haynes and Milne, 2001; Licht et al., 2000, 1999; Mitchell et al., 2004; Mitchell, 2003; Ozdemir, 2005; Quesnele et al., 2014; Rivett et al., 1999, 2003; Sakaguchi et al., 2003; Sultan et al., 2009; Thiel et al., 1994; Thomas et al., 2015, 2013; Weintraub and Khoury, 1995; Zaina et al., 2003) and the combination of maximum rotation and extension (n=7)(Arnold et al., 2004; Côté et al., 1996; Licht et al., 2000; Rivett et al., 1999; Sultan et al., 2009; Thiel et al., 1994) were the cervical positions tested most frequently. Vascular test manoeuvres as described by Wallenberg or De Kleijn which are all combinations of maximum rotation and extension were included in the latter position.(Côté et al., 1996) Other cervical positions in which the vertebral artery was

tested were maximum rotation and distraction; maximum rotation at C1-2(Thomas et al., 2013); rotation 5-15° (Thiel et al., 1994); rotation 30° (Ozdemir, 2005); rotation 45° (Haynes and Milne, 2001; Licht et al., 2000; Quesnele et al., 2014; Zaina et al., 2003); rotation 60° (Niewiadomski et al., 2017),maximum extension(Arnold et al., 2004; Rivett et al., 2003; Thiel et al., 1994; Weintraub and Khoury, 1995; Yi-Kai et al., 1999); maximum extension and 45° rotation(Araz Server et al., 2018); maximum extension, maximum rotation and distraction(Licht et al., 2000); pre-manipulative positions at C1-2(Arnold et al., 2004; Bowler et al., 2011; Erhardt et al., 2015); maximum flexion and maximum rotation(Sultan et al., 2009); distraction(Creighton et al., 2017); and a post-test in neutral(Zaina et al., 2003).

For the carotid artery, maximum rotation (n=4)(Rivett et al., 1999; Thomas et al., 2015, 2013; Weintraub and Khoury, 1995) was also most frequently tested, followed by maximal extension and maximum rotation (n=2)(Licht et al., 2002; Rivett et al., 1999). Other described cervical positions for the carotid artery were: maximum rotation and distraction; maximum rotation at C1-2; rotation 45°; maximum extension; pre-manipulative positions; a semi-fowler position, extension and 10° collateral rotation; and a post-test in neutral.

The intracranial arteries were most frequently tested in maximum rotation (n=6) (Hedera et al., 1993; Petersen et al., 1996; Sturzenegger et al., 1994; Sultan et al., 2009; Thomas et al., 2013) and maximum extension (n=3)(Siwach et al., 2016; Sturzenegger et al., 1994; Weintraub and Khoury, 1995). The other cervical positions for this artery included maximum rotation and distraction(Thomas et al., 2013); maximum rotation at C1-2(Thomas et al., 2013); extension and maximum rotation(Hedera et al., 1993; Sultan et al., 2009); maximum flexion(Siwach et al., 2016; Sturzenegger et al., 1994); maximum flexion and maximum rotation(Sultan et al., 2009); distraction(Thomas et al., 2013); and a post-test in neutral(Petersen et al., 1996).

HEMODYNAMIC CHANGES:

Thirteen studies(Creighton et al., 2017; Erhardt et al., 2015; Haynes et al., 2002; Haynes and Milne, 2001; Licht et al., 2002, 2000, 1999; Niewiadomski et al., 2017; Quesnele et al., 2014; Rivett et al., 2003; Siwach et al., 2016; Sultan et al., 2009; Thomas et al., 2013; Yi-Kai et al., 1999) mentioned no significant hemodynamic change for all included cervical positions, whereas two studies(Mitchell, 2003; Sakaguchi et al., 2003) mentioned a significant hemodynamic decrease for all included cervical positions. The majority of studies noted no significant hemodynamic changes during maximum rotation (n=16).(Arnold et al., 2004; Haynes et al., 2002; Haynes and

Milne, 2001; Licht et al., 2000, 1999; Mitchell et al., 2004; Ozdemir, 2005; Quesnele et al., 2014; Rivett et al., 2003, 1999; Sakaguchi et al., 2003; Sultan et al., 2009; Thiel et al., 1994; Thomas et al., 2015, 2013; Zaina et al., 2003) The significant changes that were most commonly identified for the vertebral artery were hemodynamic decrease in maximum rotation (n=8)(Arnold et al., 2004; Mitchell et al., 2004; Mitchell, 2003; Ozdemir, 2005; Rivett et al., 1999; Sakaguchi et al., 2003; Thomas et al., 2015; Weintraub and Khoury, 1995) and combined movement of maximum extension and maximum rotation (n=4)(Arnold et al., 2004; Côté et al., 1996; Rivett et al., 1999; Thiel et al., 1994). A similar pattern was also identified for maximum rotation and combined movement of maximum extension and maximum rotation in relation to the hemodynamics of internal carotid and intracranial arteries. One study mentioned an increase in peak flow velocity and time averaged mean flow velocity in the carotid artery.(Saracoglu et al., 2016) However, this was post-induction in a pre-surgery situation.

A specification of all cervical positions combined with the hemodynamic changes specified per artery can be found in Appendix 1.

SUBGROUP ANALYSES

Twenty-two studies used groups with healthy participants.(Araz Server et al., 2018; Arnold et al., 2004; Bowler et al., 2011; Côté et al., 1996; Erhardt et al., 2015; Haynes et al., 2002; Hedera et al., 1993; Licht et al., 1999; Mitchell et al., 2004; Mitchell, 2003; Niewiadomski et al., 2017; Ozdemir, 2005; Petersen et al., 1996; Quesnele et al., 2014; Rivett et al., 2003, 1999; Thiel et al., 1994; Thomas et al., 2015, 2013; Weintraub and Khoury, 1995; Yi-Kai et al., 1999; Zaina et al., 2003) Eleven studies used groups with people with vascular pathology.(Côté et al., 1996; Licht et al., 2002, 2000; Niewiadomski et al., 2017; Ozdemir, 2005; Petersen et al., 1996; Rivett et al., 1999; Sakaguchi et al., 2003; Sturzenegger et al., 1994; Sultan et al., 2009; Thiel et al., 1994; Weintraub and Khoury, 1995) Five studies mentioned non-vascular participant groups.(Araz Server et al., 2018; Haynes and Milne, 2001; Ozdemir, 2005; Saracoglu et al., 2016; Siwach et al., 2016) For one study it was unclear whether the participants were healthy or had a pathology.(Creighton et al., 2017) A comparison of the groups with people including vascular pathology and groups of other patients shows that there were proportionally no differences.

Manipulations were mentioned for the vertebral artery only.(Erhardt et al., 2015; Quesnele et al., 2014) Both studies scored well in our risk of bias assessment except for sample size. Quesnele et al.(Quesnele et al., 2014) included 10 healthy

participants and Erhardt(Erhardt et al., 2015) 23 participants. Therefore, they both scored moderate for sample size. (Table 2, Risk of bias) Pre-manipulative position was mentioned for the vertebral artery in three studies(Arnold et al., 2004; Bowler et al., 2011; Erhardt et al., 2015) and in one study(Bowler et al., 2011) for the carotid artery. Arnold et al. was the only study that reported a pre-manipulative position significantly decreased the velocity and resistance index.(Arnold et al., 2004) However, this was not found for both arteries in left and right rotation. Bowler et al. mentioned a significant decrease of the resistance index, but not for the Peak Systolic Velocity (PSV), End Diastolic Velocity (EDV) and mean Velocity.(Bowler et al., 2011) The other study mentioned no significant difference in flow velocities or resistance index.(Erhardt et al., 2015)

RISK OF BIAS

The results are presented in table 2. No studies scored a high risk of bias. Seven articles(Arnold et al., 2004; Creighton et al., 2017; Mitchell et al., 2004; Mitchell, 2003; Niewiadomski et al., 2017; Ozdemir, 2005; Sakaguchi et al., 2003) scored no risk of bias and no article scored positive on more than two of the seven parts of the assessment tool. Risk of bias due to a moderate or small sample size was found in 20 studies(Araz Server et al., 2018; Bowler et al., 2011; Côté et al., 1996; Erhardt et al., 2015; Haynes et al., 2002; Haynes and Milne, 2001; Licht et al., 2002, 2000, 1999; Mitchell et al., 2004; Quesnele et al., 2014; Rivett et al., 2003, 1999; Saracoglu et al., 2016; Sturzenegger et al., 1994; Sultan et al., 2009; Thiel et al., 1994; Thomas et al., 2015, 2013; Zaina et al., 2003). Risk of bias due to inadequate sample size (item 3) was found in four studies (Arnold et al., 2004; Creighton et al., 2017; Mitchell, 2003; Weintraub and Khoury, 1995). Risk of bias as a result of inadequate described objective or hypothesis was found in six studies(Licht et al., 1999; Sturzenegger et al., 1994; Sultan et al., 2009; Weintraub and Khoury, 1995; Yi-Kai et al., 1999; Zaina et al., 2003). One study missed a detailed description of the interventions for each group.(Côté et al., 1996)

Table 2. Risk of Bias

Author(s) & year	*1) Specific objectives or hypotheses*	*2) Eligibility criteria for participants*	*3) Sample size*	*4) Detailed description of interventions for each group*	*5) Test conditions similar for all measurements*	*6) Prespecified primary and secondary outcome measures*	*7) All of the predefined outcomes were specified in the results section*	*Total score*
(Hedera et al., 1993)	0	0	1	0	0	0	0	1
(Sturzenegger et al., 1994)	1	0	3	0	0	0	0	4
(Thiel et al., 1994)	0	0	2	0	0	0	0	2
(Weintraub and Khoury, 1995)	1	0	0	0	0	0	0	1
(Côté et al., 1996)	0	0	2	1	0	0	0	3
(Petersen et al., 1996)	0	0	1	0	0	0	0	1
(Licht et al., 1999)	1	0	3	0	0	0	0	4
(Rivett et al., 1999)	0	0	3	0	0	0	0	3
(Yi-Kai et al., 1999)	1	0	1	0	0	0	0	2
(Licht et al., 2000)	0	0	3	0	0	0	0	3
(Haynes and Milne, 2001)	0	0	3	0	0	0	0	3

(Haynes et al., 2002)	0	0	3	0	0	0	0	3
(Licht et al., 2002)	0	0	3	0	0	0	0	3
(Mitchell, 2003)	0	0	0	0	0	0	0	0
(Rivett et al., 2003)	0	0	3	0	0	0	0	3
(Sakaguchi et al., 2003)	0	0	0	0	0	0	0	0
(Zaina et al., 2003)	1	0	3	0	0	0	0	4
(Arnold et al., 2004)	0	0	0	0	0	0	0	0
(Mitchell et al., 2004)	0	0	3	0	0	0	0	0
(Ozdemir, 2005)	0	0	1	0	0	0	0	0
(Sultan et al., 2009)	1	0	2	0	0	0	0	3
(Bowler et al., 2011)	0	0	3	0	0	0	0	3
(Thomas et al., 2013)	0	0	3	0	0	0	0	3
(Quesnele et al., 2014)	0	0	3	0	0	0	0	3
(Erhardt et al., 2015)	0	0	3	0	0	0	0	3

Table 2. Continued

Author(s) & year	*1) Specific objectives or hypotheses*	*2) Eligibility criteria for participants*	*3) Sample size*	*4) Detailed description of interventions for each group*	*5) Test conditions similar for all measurements*	*6) Prespecified primary and secondary outcome measures*	*7) All of the predefined outcomes were specified in the results section*	*Total score*
(Thomas et al., 2015)	0	0	3	0	0	0	0	3
(Siwach et al., 2016)	0	0	1	0	0	0	0	1
(Saracoglu et al., 2016)	0	0	2	0	0	0	0	2
(Araz Server et al., 2017)	0	0	2	0	0	0	0	2
(Creighton et al., 2017)	0	0	0	0	0	0	0	0
(Niewiadomski et al., 2017)	0	0	0	0	0	0	0	0

Scoring questions 1,2,4,5,6&7: 'Yes' or 'Not Applicable' = 0 points; 'No' or 'Can't answer' = 1 point.
Scoring question 3: 'Adequate sample size' (≥100) = 0 points; 'Good sample size' (50-99) = 1 point; 'Moderate sample size' (30-49) = 2 points; 'Small sample size' (<30) = 3 points

DISCUSSION

SUMMARY OF MAIN FINDINGS.

The data synthesized from 31 experimental and quasi-experimental studies suggest that in most people cranio-cervical positions and movements had no effect on blood flow. In a small proportion of the groups 'healthy subjects', 'vascular patients', and 'other patients', blood flow does decrease during some movements, specifically maximal rotation and/or extension. The positions and movements utilised in high velocity thrust techniques do not seem to alter blood flow. A clinical implication from this review is that the relationship between cranio-cervical movement and alterations in blood flow does not seem to be as obvious as previous data suggested. Considering blood flow as a robust measure of vessel stress, based on these data it is unlikely that head and neck movement alone, even if forceful, could mechanistically explain the aetiology of adverse events which have conventionally been purported to be related to therapeutic interventions.

Hemodynamic parameters act as a proxy measure for mechanical stress on cervical arteries. The rationale for vessel stress in healthy persons and patients with vascular pathology is similar. When stress is applied to a vessel the diameter changes and can alter the blood flow velocity or volume. Therefore, when a cervical positional change puts stress on a vessel, it should theoretically also change the hemodynamics. Most studies reported no change in hemodynamic parameters during any tested movements and positions, in both healthy and vascular/other groups. Some studies reported hemodynamic changes during maximal rotation and extension when performed in either isolation or when combined. There were more positions found to influence hemodynamic parameters in studies which included people with vascular pathology and other patients. Overall, the pattern of hemodynamic responses to cervical position and movement seems to be a naturally occurring phenomenon related to the anatomy of the cervico-cranial region. This conclusion is supported by both the high proportion of studies which demonstrate no changes at all in any groups, together with the proportion which show changes in healthy subjects. The differences in hemodynamic parameters between healthy and vascular/other subjects are only in terms of the number of positions where changes were identified. Conventional thought within the domain of manual therapy has been that rapid, forceful interventions such as HVT techniques are considered to constitute a higher risk for neuro-vascular events resulting from cervical arterial compromise. However, we found that studies which focussed specially on HVT reported no hemodynamic changes. Furthermore, studies that reported positioning and movement were not unambiguous in reporting hemodynamic changes.

Various studies investigated hemodynamics in single or multiple cervical positions, a single artery, or treatment technique.(Kerry et al., 2008; Mitchell, 2009) However, these data had not been previously synthesised. Our findings are similar to the conclusions of previous reviews on this topic. Mitchell 2009 conducted a meta-analysis of data from nine studies (n=204 subjects) and reported that contralateral rotation was the movement most commonly associated with a reduction of flow parameters.(Mitchell, 2009) This occurred more so in patients than it did in healthy subjects. Mitchell also reported that those studies which recorded symptom reproduction (specifically for vertebral artery insufficiency) in patients during the compromising movement were unable to establish an association between flow change and symptoms. This observation would have implications for the validity of testing procedures which rely on this underlying mechanism, e.g. functional positional tests. In our review, the recording of symptom reproduction in the included studies was insufficient to allow drawing any conclusions in line with Mitchell. This might be explained by the broader inclusion criteria and the studies published after 2009. We included 23 studies for the vertebral artery vs nine in Mitchell's study. (Mitchell, 2009) Hutting et al. reviewed four blood flow studies (n=1271) to examine the concept of diagnostic accuracy of functional positional testing.(Nathan Hutting et al., 2013) They too were unable to establish a relationship between flow changes and symptom reproduction. The aim of these vascular integrity test procedures is to unilaterally compress an artery to test the contralateral blood supply. However, when examining our data, it is plausible that testing based on this mechanism does not appear to be a valid construct. Therefore, the rationale and value of the tests should be questioned. Hemodynamic patterns in Mitchells study were in agreement with those found in the current review. (Mitchell, 2009)

The present data has potential clinical implications for the use of therapeutic interventions for the management of people with head and neck pain. There appears to be no consistently reported positions which induce greater hemodynamic responses than others. The two studies that focussed on HVT did not find a hemodynamic effect either.(Erhardt et al., 2015; Quesnele et al., 2014) However, it cannot be ruled out that rapid, forceful movements might also be a trigger for vascular wall trauma which is not identifiable through measurement of the parameters included in this current review. We therefore cannot conclude that all interventions are equally safe especially since the two studies had a moderate sample size.(Erhardt et al., 2015; Quesnele et al., 2014) This point is in agreement with the key developments highlighted in the latest International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) practice framework, which

promotes a more holistic consideration of risk management, including factors other than just effect of a specific intervention, e.g. underlying pathology, cardio-vascular risk factors, etc.(Rushton et al., 2014) The present data supports this reasoning which suggests that adverse events related to cervical spine interventions might be the result of something other than the therapeutic positioning or movement of the head and neck. Clinicians should be mindful however that there may be small sub-groups of the population with underlying arterial pathology whereby the small hemodynamic changes may be sufficient to induce or exacerbate serious neuro-vascular compromise. Therefore, it might be wise to choose treatment techniques first in positions with less than 45 degrees of cervical rotation since the data of the included studies is most consistent in these positions.

REVIEW LIMITATIONS

We considered a number of possibilities to providing a meaningful quality assessment, but due to the wide variation of study type, no reference standard for what constitutes high quality for the constituent variables of these particular methods, and a lack of focus towards a specific intervention or diagnosis, a suitable validated tool was not available. Given the importance of assessing the risk of bias, the authors developed a new tool as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*.(Higgins et al., 2011; Katikireddi et al., 2015) Development was based on the Delphi principle. The primary concept of the tool was based on literature and reviewed in two more rounds.(Hasson et al., 2000) Seven studies(Arnold et al., 2004; Creighton et al., 2017; Mitchell et al., 2004; Mitchell, 2003; Niewiadomski et al., 2017; Ozdemir, 2005; Sakaguchi et al., 2003) scored no risk of bias and none of the others scored a risk of bias at more than 3 of the 7 points. In general, no study scored a high risk of bias. Most reported bias was a small sample size. Although this quality tool was developed thoughtfully, it did not detect ambiguities in the study of Niewiadomski et al.(Niewiadomski et al., 2017) The authors did not present all data to substantiate their conclusions and did not respond to an email requesting further explanation. A second limitation is the lack of quantifiable change, in terms of unit measurement. The heterogeneity and variety of flow and velocity parameters identified means that a standardized unit suitable for comparisons or judgements of effect size cannot be made. Due to this methodological diversity we decided to conduct a high quality synthesis instead of a meta-analysis.(Grindem et al., 2018) Further, there is no *a priori* reference standard for what constitutes significant change when using blood flow parameters as a proxy measure for vessel stress.

For future research we advise authors to report all data available, such as standard deviations, confidence intervals and all hemodynamic outcomes. The availability of these parameters would enhance the ability to perform a meta-analysis.

CONCLUSION

Our results suggest that in most people, healthy as well as patients with vascular pathologies, cranio-cervical positions do not alter cervical blood flow. This includes vascular test positions, pre-manipulative positions and manipulations.

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APPENDIX

Cervical positional influences on VERTEBRAL ARTERIAL velocity or volume

How to read this table?
In the upper row of the table the vertebral haemodynamic effects of a maximum cervical rotation to the left are summarized and specified. In the first column it describes that study with reference 1-5 state that there is no significant change in PSV for the left vertebral artery. However, also that 1 study (ref 10) states a significant decrease in PSV for this movement and artery. As you continue down the row you can see that references 1-5, 9,15 & 16 state no significant changes and reference 10 & 18 state a significant decrease in the right vertebral artery during the same movement.
" =" indicates no significant change, " – " a significant decrease and " + " *a significant increase.*

		Peak Systolic Velocity (PSV)	***End Diastolic. Velocity (EDV)***	***Mean Flow Velocity (time average)***	***Mean Peak Flow Velocity***	***Arterial Diameter***	***Ratio PSV/EDV***	***Resistance Index***	***Blood Flow Volume***	***Blood Flow Volume Rate***	***Blood Flow Velocity Ratio's***
Rotation	max LEFT		L = (1–5)	L = (1,2,4,5)	L = (2,3)	L = (1)			L = (1,5)	L = (6–8)	L = (9)
			L – (10)		L – (11,12)	L – (13)	L – (14)			L – (10,12)	
			R = (1–5,9,15,16)	R = (1,2,4,15,16)	R = (2,3,15,16)	R = (1,13)	R = (15)	R = (15,17)	R = (1,15)	R = (7,8,10,15)	R = (9)
			R – (10,18)	R – (5,18)	R – (11,12)		R – (14)		R – (5,18)	R - (6,12)	

	Peak Systolic Velocity (PSV)	*End Diastolic. Velocity (EDV)*	*Mean Flow Velocity (time average)*	*Mean Peak Flow Velocity*	*Arterial Diameter*	*Ratio PSV/EDV*	*Resistance Index*	*Blood Flow Volume*	*Blood Flow Volume Rate*	*Blood Flow Velocity Ratio's*
max RIGHT		L = (1–5,9,15,16)	L = (1,2,4,15,16)	L = (2,3,15,16)	L = (1,13)	L = (15)	L = (15,17)	L = (1,15,18)	L = (6–8,15)	
		L – (10,18)	L – (5,18)	L – (11)		L – (14)		L – (5)	L – (10)	
		R = (1–5)	R = (1,2,4,5)	R = (2,3)	R = (1,13)	R – (14)		R = (1,5)	R = (6–8,10)	
		L – (10)		R – (11)						
max LEFT + distraction									L = (7)	
									R = (7)	
max RIGHT + distraction									L = (7)	
									R = (7)	
C1-2 max LEFT									L = (7)	
									R = (7)	

	Peak Systolic Velocity (PSV)	*End Diastolic. Velocity (EDV)*	*Mean Flow Velocity (time average)*	*Mean Peak Flow Velocity*	*Arterial Diameter*	*Ratio PSV/EDV*	*Resistance Index*	*Blood Flow Volume*	*Blood Flow Volume Rate*	*Blood Flow Velocity Ratio's*
C1-2 max RIGHT									L = (7) R = (7)	
5-15 dgr LEFT							R = (17)			
5-15 dgr RIGHT							R = (17)			
30 dgr LEFT		L – (10) R – (10)							L – (10) R = (10)	
30 dgr RIGHT		L – (10) R – (10)							L – (10) R = (10)	
45 dgr LEFT		L = (1–3) R = (1–3,9,18)	L = (1,2) R = (1,2,18)	L = (2,3) R = (2,3)	L = (1) R = (1)			L = (1) R = (1,18)	L = (8) R = (8)	R = (9)

		Peak Systolic Velocity (PSV)	*End Diastolic. Velocity (EDV)*	*Mean Flow Velocity (time average)*	*Mean Peak Flow Velocity*	*Arterial Diameter*	*Ratio PSV/EDV*	*Resistance Index*	*Blood Flow Volume*	*Blood Flow Volume Rate*	*Blood Flow Velocity Ratio's*
	45 dgr RIGHT		L = (1–3,9,18)	L = (1,2,18)	L = (2,3)	L = (1)			L = (1,18)	L = (8)	L = (9)
			R = (1–3)	R = (1,2)	R = (2,3)	R = (1)			R = (1)	R = (8)	
	60 dgr LEFT		L = (19)	L = (19)							
			R = (19)	R = (19)							
	60 dgr RIGHT		L = (19)	L = (19)							
			R = (19)	R = (19)							
Extension	max		L = (5,15,20)	L = (5,15,20)	L = (15,20)		L = (15)	R = (17)	L = (5,15,20)	L = (15)	L = (15)
					L – (12)					L – (12)	
			R = (5,15,20)	R = (5,15,20)	R = (15,20)		R = (15)	R = (17)	R = (5,15,20)	R = (15)	R = (15)
					R – (12)					R – (12)	

		Peak Systolic Velocity (PSV)	*End Diastolic. Velocity (EDV)*	*Mean Flow Velocity (time average)*	*Mean Peak Flow Velocity*	*Arterial Diameter*	*Ratio PSV/EDV*	*Resistance Index*	*Blood Flow Volume*	*Blood Flow Volume Rate*	*Blood Flow Velocity Ratio's*
	max + rotation 45 dgr LEFT					L = (21)			L – (21)		
									L = (21)		
						R = (21)			R = (21)		
	max + rotation 45 dgr RIGHT					L = (21)			L = (21)		
						R = (21)			R = (21)		
									R – (21)		
Extension max + Rotation max[1]	LEFT		L = (2,4,5,20)	L = (4,5,18,20)	L = (2,20)			L = (5,20)			L = (22)
								L – (5)			
			R = (2,4,5,20)	R = (4,5,18,20)	R = (2,20)		R = (17,18)	R = (5,20)			R – (22)
			R – (18)	R – (18)			R – (18)				

[1] Including the manoeuvres as described by Wallenberg or De Kleijn (32)

		Peak Systolic Velocity (PSV)	*End Diastolic. Velocity (EDV)*	*Mean Flow Velocity (time average)*	*Mean Peak Flow Velocity*	*Arterial Diameter*	*Ratio PSV/EDV*	*Resistance Index*	*Blood Flow Volume*	*Blood Flow Volume Rate*	*Blood Flow Velocity Ratio's*
	RIGHT		L = (2,4,5)	L = (4,5,18)	L = (2)			L – (17)	L = (5)		L = (22)
			L – (18)	L – (18)				L = (18)			
			R = (2,4,5)	R = (4,5)	R = (2)				R = (5)		R = (22)
									R – (5)		
Extension max +Rotation max + distraction	LEFT		L = (2)	L = (2)					L = (2)		
			R = (2)	R = (2)					R = (2)		
	RIGHT		L = (2)	L = (2)					L = (2)		
			R = (2)	R = (2)					R = (2)		

		Peak Systolic Velocity (PSV)	*End Diastolic. Velocity (EDV)*	*Mean Flow Velocity (time average)*	*Mean Peak Flow Velocity*	*Arterial Diameter*	*Ratio PSV/EDV*	*Resistance Index*	*Blood Flow Volume*	*Blood Flow Volume Rate*	*Blood Flow Velocity Ratio's*
Pre-manipulative position	LEFT		L = (5,23)	L = (23)	L = (23)				L = (5)		
				L – (5)					L – (23)		
			R = (23)	R = (23)	R = (23)						
			R – (5)	R – (5)					R – (5,23)		
	RIGHT		L = (23)	L = (23)	L = (23)				L = (23)		
			L – (5)	L – (5)					L – (5)		
			R = (5,23,24)	R = (23,24)	R = (23,24)	R = (23,24)			R = (5,24)		
				R – (5)					R – (23)		
Manipulation C1-2	LEFT		L = (3)		L = (3)						
			R = (3)		R = (3)						

		Peak Systolic Velocity (PSV)	*End Diastolic. Velocity (EDV)*	*Mean Flow Velocity (time average)*	*Mean Peak Flow Velocity*	*Arterial Diameter*	*Ratio PSV/EDV*	*Resistance Index*	*Blood Flow Volume*	*Blood Flow Volume Rate*	*Blood Flow Velocity Ratio's*
	RIGHT		L = (3)		L = (3)						
			R = (3,24)	R = (24)	R = (3,24)	R = (24)			R = (24)		
Flexion max + rotation max	LEFT		L = (4)	L = (4)							
			R = (4)	R = (4)							
	RIGHT		L = (4)	L = (4)							
			R = (4)	R = (4)							
Distraction			L = (25)	L = (25)						L = (7)	
			R = (25)	R = (25)						R = (7)	
Post-test	neutral		L – (9)							L = (7)	L = (9)
			R = (9)							R = (7)	R = (9)

Cervical positional influences on CAROTID ARTERIAL velocity or volume.

		Peak Systolic Velocity (PSV)	***End Diastolic. Velocity (EDV)***	***Mean Flow Velocity (time average)***	***Arterial Diameter***	***Resistance Index***	***Blood Flow Volume***	***Commom Carotid Volume***
Rotation	max LEFT			L = (12)			L = (6,7,12)	
		R = (18)	R= (18)	R = (12)		R = (18)	R = (7,12)	
		R – (18)	R – (18)				R – (6,7)	
	max RIGHT	L = (18)	L = (18)	L = (12)		L = (18)	L = (6,12)	
				R = (12)			R = (6,7,12)	
	max LEFT + distraction						L = (7)	
							R = (7)	
	max RIGHT + distraction						L = (7)	
							R = (7)	
	C1-2 max LEFT						L = (7)	
							R = (7)	
	C1-2 max RIGHT						L = (7)	
							R = (7)	
	45 dgr LEFT	R = (18)	R = (18)			R = (18)		
	45 dgr RIGHT	L = (18)	L = (18)			L = (18)		

		Peak Systolic Velocity (PSV)	***End Diastolic. Velocity (EDV)***	***Mean Flow Velocity (time average)***	***Arterial Diameter***	***Resistance Index***	***Blood Flow Volume***	***Commom Carotid Volume***
Extension	max			L = (12)			L = (12)	
				R = (12)			R = (12)	
Extension max + Rotation max[2]	LEFT	L = (26)		L = (26)				
		R = (26)		R = (26)		R = (18)		
		R - (18)	R - (18)					
	RIGHT	L = (18,26)	L = (18)	L = (26)		L = (18)		
		R = (26)		R = (26)				
Distraction							L = (7)	
							R = (7)	
Semi Fowler	extension + 10 dgr collateral rotation – post-induction	L + (27)		L + (27)	L = (27)			L – (27)
	extension + 10 dgr collateral rotation - post-surgery	L – (27)		L – (27)	L = (27)			L – (27)
Post-test	neutral						L = (7)	
							R = (7)	

[2] Including the manoeuvres as described by Wallenberg or De Kleijn (32)

Cervical positional influences on INTRACRANIAL ARTERIAL velocity or volume.

		Peak Systolic Velocity (PSV)	***End Diastolic. Velocity (EDV)***	***Mean Flow Velocity (time average)***	***Resistance Index***	***Mean Peak Flow Velocity***	***Blood Flow Volume***
Rotation	max LEFT	L = (4)	L = (4)	L = (12,28,29)	L = (30)		L = (7,12)
				L – (28,30)			
		R = (4)	R = (4)	R = (12,28,29)			R = (7,12)
				R – (28,30)	R – (30)		
	max RIGHT	L = (4)	L = (4)	L = (12,28,29)			L = (7,12)
				L – (28,30)	L – (30)		
		R = (4)	R = (4)	R = (12,28,29)	R = (30)		R = (7,12)
				R – (28,30)			
	max LEFT + distraction						L = (7)
							R = (7)
	max RIGHT + distraction						L = (7)
							R = (7)
	C1-2 max LEFT						L = (7)
							R = (7)
	C1-2 max RIGHT						L = (7)
							R = (7)

		Peak Systolic Velocity (PSV)	***End Diastolic. Velocity (EDV)***	***Mean Flow Velocity (time average)***	***Resistance Index***	***Mean Peak Flow Velocity***	***Blood Flow Volume***
Extension	max			L = (12)		L = (31)	L = (12)
				L = (29)		R = (31)	
				R = (12)			R = (12)
				R – (29)			
Extension max + Rotation max[3]	LEFT	L = (4)	L = (4)				
					L – (30)		
		R = (4)	R = (4)		R = (30)		
	RIGHT				L= (30)		
					R- (30)		
Flexion	max					L = (29,31)	
						R = (29,31)	
	max + rotation max LEFT	L = (4)	L = (4)				
		R = (4)	R = (4)				
	max + rotation max RIGHT	L = (4)	L = (4)				
		R = (4)	R = (4)				
Distraction							L = (7)
							R = (7)

[3] Including the manoeuvres as described by Wallenberg or De Kleijn (32)

		Peak Systolic Velocity (PSV)	***End Diastolic. Velocity (EDV)***	***Mean Flow Velocity (time average)***	***Resistance Index***	***Mean Peak Flow Velocity***	***Blood Flow Volume***
Post-test	neutral			L = (28)			
				R = (28)			

Abbreviations:
L: Left; R: Right; + Significant increase (green); = No significant change (orange); - Significant decrease (red)

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APPENDIX 2: SEARCH STRATEGIES

PUBMED:

("Neck"[Mesh] OR "Rotation"[Mesh] OR "Musculoskeletal Manipulations"[Mesh] OR "Cervical spine"[Title/Abstract] OR Neck[Title/Abstract] OR Head[Title/Abstract] OR Mobilization[Title/Abstract] OR Mobilisation[Title/Abstract] OR Extension*[Title/Abstract] OR Flexion*[Title/Abstract] OR Rotation*[Title/Abstract] OR Distraction*[Title/Abstract] OR Manipulation*[Title/Abstract] OR Midrange*[Title/Abstract] OR Mid-range*[Title/Abstract] OR Premanipulat*[Title/Abstract] OR Pre-manipulat*[Title/Abstract]) AND ("Vertebral Artery"[Mesh] OR "Carotid Arteries"[Mesh] OR "Carotid Artery, internal"[Mesh] OR "Vertebrobasilar Insufficiency"[Mesh] OR Vertebral Arter*[Title/Abstract] OR Carotid Arter*[Title/Abstract] OR vertebrobasilar insufficienc*[Title/Abstract]) AND ("Hemodynamics"[Mesh] OR "Blood Circulation"[Mesh] OR "Blood Flow Velocity"[Mesh] OR "Regional Blood Flow"[Mesh] OR "blood supply" [Subheading] OR hemodynamic*[Title/Abstract] OR Blood flow*[Title/Abstract] OR Bloodflow[Title/Abstract] OR Blood circulat*[Title/Abstract] OR Blood suppl*[Title/Abstract] OR "Flow in"[Title/Abstract] OR Inflow*[Title/Abstract] OR Flow velocit*[Title/Abstract] OR Arterial pressur*[Title/Abstract] OR Test*[Title/Abstract]) AND ("Ultrasonography"[Mesh] OR "Ultrasonography, Doppler"[Mesh] OR "Ultrasonography, Doppler, Color"[Mesh] OR "Magnetic Resonance Angiography"[Mesh] OR "Magnetic Resonance Imaging"[Mesh] OR "Coronary AngiWography"[Mesh] OR "Ultrasonography"[Title/Abstract] OR "Ultrasound"[Title/Abstract] OR "Ultrasound imaging"[Title/Abstract] OR "Medical sonography"[Title/Abstract] OR "Ultrasonic imaging"[Title/Abstract] OR "Echography"[Title/Abstract] OR "Doppler"[Title/Abstract] OR "MRI"[Title/Abstract] OR "Magnetic Resonance Imaging"[Title/Abstract] OR "MRA"[Title/Abstract] OR "Magnetic Resonance Angiography"[Title/Abstract])

CINAHL:

((MH ("Neck" OR "Rotation") OR TI ("Cervical spine" OR Neck OR Head OR Mobilization OR Mobilisation OR Extension* OR Flexion* OR Rotation* OR Distraction* OR Manipulation* OR Midrange* OR Mid-range* OR Premanipulat* OR Pre-manipulat*) OR AB ("Cervical spine" OR Neck OR Head OR Mobilization OR Mobilisation OR Extension* OR Flexion* OR Rotation* OR Distraction* OR Manipulation* OR Midrange* OR Mid-range* OR Premanipulat* OR Pre-manipulat*)) AND ((MH ("Vertebral Artery" OR "Carotid Arteries") OR TI (Vertebral Arter* OR Carotid Arter* OR vertebrobasilar insufficienc*) OR AB (Vertebral Arter* OR Carotid Arter* OR vertebrobasilar insufficienc*)) AND ((MH ("Hemodynamics" OR "Blood Circulation"

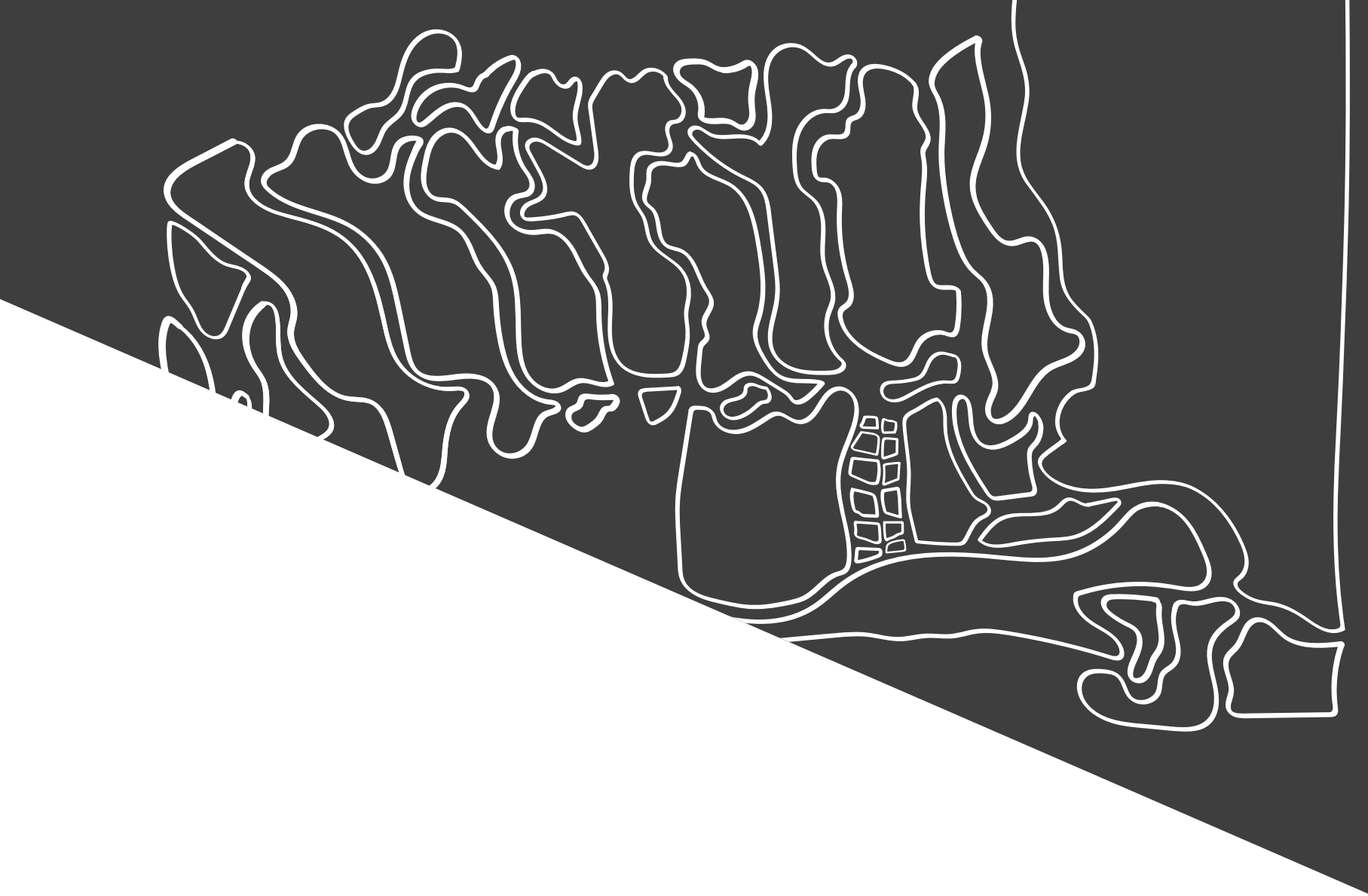
OR “Blood Flow Velocity”) OR TI (hemodynamic* OR Blood flow* OR Bloodflow OR Blood circulat* OR Blood suppl* OR “Flow in” OR Inflow* OR Flow velocit* OR Arterial pressur* OR Test*) OR AB (hemodynamic* OR Blood flow* OR Bloodflow OR Blood circulat* OR Blood suppl* OR “Flow in” OR Inflow* OR Flow velocit* OR Arterial pressur* OR Test*)) AND ((MH (“Ultrasonography” OR “Ultrasonography, Doppler, Color” OR “Ultrasonography, Doppler” OR “Magnetic Resonance Angiography” OR “Magnetic Resonance Imaging” OR “Coronary Angiography”) OR TI (“Ultrasonography” OR “Ultrasound” OR “Ultrasound imaging” OR “Medical sonography” OR “Ultrasonic imaging” OR “Echography” OR “Doppler” OR “MRI” OR “Magnetic Resonance Imaging” OR “MRA” OR “Magnetic Resonance Angiography”) OR AB (“Ultrasonography” OR “Ultrasound” OR “Ultrasound imaging” OR “Medical sonography” OR “Ultrasonic imaging” OR “Echography” OR “Doppler” OR “MRI” OR “Magnetic Resonance Imaging” OR “MRA” OR “Magnetic Resonance Angiography”))

Embase:

(‘neck’/mj OR ‘rotation’/exp OR ‘Cervical spine’:ab,ti OR Neck:ab,ti OR Head:ab,ti OR Mobilization:ab,ti OR Mobilisation:ab,ti OR Extension:ab,ti OR Extensions:ab,ti OR Flexion:ab,ti OR Flexions:ab,ti OR Rotation:ab,ti OR Rotations:ab,ti OR Distraction:ab,ti OR Distractions:ab,ti OR Manipulation:ab,ti OR Manipulations:ab,ti OR Midrange:ab,ti OR Mid-range:ab,ti OR Premanipulation:ab,ti OR Pre-manipulation:ab,ti) AND (‘vertebral artery’/exp OR ‘carotid artery’/exp OR ‘basilar artery’/exp OR ‘Vertebral Artery’:ab,ti OR ‘Vertebral Arteries’:ab,ti OR ‘Carotid Artery’:ab,ti OR ‘Carotid Arteries’:ab,ti OR ‘Basilar Artery’:ab,ti OR ‘Basilar Arteries’:ab,ti OR ‘vertebrobasilar insufficiency’:ab,ti OR ‘vertebrobasilar insufficiencies’:ab,ti) AND (‘hemodynamics’/mj OR ‘arterial circulation’/exp OR ‘blood flow velocity’/exp OR Hemodynamic:ab,ti OR Hemodynamics:ab,ti OR ‘arterial circulation’:ab,ti OR ‘Blood flow’:ab,ti OR ‘Blood flowing’:ab,ti OR Bloodflow:ab,ti OR Bloodflowing:ab,ti OR ‘Blood circulation’:ab,ti OR ‘Blood supply’:ab,ti OR ‘Blood supplies’:ab,ti OR ‘Blood supplying’:ab,ti OR ‘Flow in’:ab,ti OR Inflow:ab,ti OR ‘Flow velocity’:ab,ti OR ‘Flow velocities’:ab,ti OR ‘Arterial pressure’:ab,ti OR ‘Arterial pressures’:ab,ti) AND (‘echography’/exp OR ‘Doppler echocardiography’/exp OR ‘Doppler ultrasonography’/exp OR ‘magnetic resonance angiography’/exp OR ‘nuclear magnetic resonance imaging’/exp OR ‘coronary angiography’/exp OR ‘Ultrasonography’:ab,ti OR ‘Ultrasound’:ab,ti OR ‘Ultrasound imaging’:ab,ti OR ‘Medical sonography’:ab,ti OR ‘Ultrasonic imaging’:ab,ti OR ‘Echography’:ab,ti OR ‘Doppler’:ab,ti OR ‘MRI’:ab,ti OR ‘Magnetic Resonance Imaging’:ab,ti OR ‘MRA’:ab,ti OR ‘Magnetic Resonance Angiography’:ab,ti OR ‘coronary angiography’:ab,ti OR ‘coronary angiographies’:ab,ti)

ICL/ MANTIS:

All Fields:Neck OR All Fields:\\\"Musculoskeletal Manipulations\\\" OR All Fields:Manipulations OR All Fields:Cervical spine OR All Fields:Head OR All Fields:Mobilization OR All Fields:Mobilisation OR All Fields:Extension OR All Fields:Flexion OR All Fields:Rotation OR All Fields:Distraction OR All Fields:Manipulation OR All Fields:Midrange OR All Fields:Mid-range OR All Fields:Premanipulat OR All Fields:Pre-manipulat AND All Fields:Vertebral Artery OR All Fields:Carotid Arteries OR All Fields:Carotid Artery, internal OR All Fields:Vertebrobasilar Insufficiency OR All Fields:Vertebral Arter* OR All Fields:Carotid Arter* OR All Fields:vertebrobasilar insufficienc* OR All Fields:VBI AND All Fields:Hemodynamics OR All Fields:Blood Circulation OR All Fields:Blood Flow Velocity OR All Fields:Regional Blood Flow OR All Fields:blood supply OR All Fields:hemodynamic* OR All Fields:Blood flow* OR All Fields:Bloodflow OR All Fields:Blood circulat* OR All Fields:Blood suppl* OR All Fields:Flow in OR All Fields:Inflow* OR All Fields:Flow velocit* OR All Fields:Arterial pressur* OR All Fields:Test* AND All Fields:Ultrasonography OR All Fields:Ultrasonography, Doppler OR All Fields:Ultrasonography, Doppler, Color OR All Fields:Coronary Angiography OR All Fields:Ultrasound OR All Fields:Ultrasound imaging OR All Fields:Medical sonography OR All Fields:Ultrasonic imaging OR All Fields:Echography OR All Fields:Doppler OR All Fields:MRI OR All Fields:Magnetic Resonance Imaging OR All Fields:MRA OR All Fields:Magnetic Resonance Angiograph



CAROTID AND VERTEBRAL ARTERIAL DISSECTIONS AFTER MANUAL PHYSICAL THERAPY: A CASE CONTROL STUDY

7

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Submitted

ABSTRACT

Introduction: Neck pain and headache are common health problems for which manual physical therapy is an effective treatment. Treatment techniques that are frequently used are mobilizations and thrust joint manipulations. In some cases, adverse events (AE) occur following these treatments. Factors influencing AE are not fully understood, but may be related to patient characteristics, clinician or the applied techniques. Thereby, incidence rates of AE have a large variation. Therefore, the objective of this study is to determine the number, type and predictors of AE following cervical treatments performed by Dutch manipulative therapists.

Method: A prospective cohort study was performed during 12 months in The Netherlands amongst clinicians using manipulative techniques. Characteristics of patients, clinicians and therapy were inventoried. Additionally, the Health and Youth Care Inspectorate (IGJ) and professional associations were asked to share reported major AE. An independent privacy monitoring board supervised the study. Descriptive techniques and robust binominal regression were applied to analyze the data.

Results: Fifty-five clinicians delivered data of 392 patients. Clinicians were averagely treating 3.5 patients per day with 0.99 manipulations, 2.86 mobilizations and 1.76 exercises during a session. No major AE were reported in our sample. Two major AE were reported at the IGJ. Minor AE were reported in 28.1% of the sessions. The indication headache and female gender of the clinician were considered significant predictors for minor AE.

Discussion: Most AE following cervical TJM are minor, the incidence for major AE is estimated at 1:2.869.020 cervical TJMs. There were no strong predictors for AE indicated.

INTRODUCTION

Neck pain is a common health problem which ranks 4th on the global burden for disability.(Hoy et al., 2014) Neck pain is considered to be a multidimensional condition that includes physical, affective, cognitive, and social aspects. A serious medical pathology is rarely the cause of neck pain (<1%).(Blanpied et al., 2017) In most cases, the pathoanatomical basis for neck pain is unclear and the pain is labeled as being nonspecific or mechanical.(de Vries et al., 2016) Clinical characteristics of neck pain can be categorized as 1] neck pain with mobility deficits; 2] neck pain with impaired movement coordination; neck pain with headache; neck pain with radiating pain; and neck pain with migraine.(Blanpied et al., 2017; Dunning et al., 2016; Gross et al., 2015) The incidence of neck pain in the general population is 16% (Kim et al., 2018) and overall prevalence is estimated around 23.1%.(Hoy et al., 2010) The latter is generally higher in woman, high income countries and rural areas.(Hoy et al., 2010) Physical manual therapy can be indicated and is an effective treatment for patients with neck pain and headache.(Coulter et al., 1996; Gross et al., 2015; Rist et al., 2019) Physical manual therapy may include mobilizations and thrust joint manipulations (TJM). The TJM is characterized by a quick thrust aiming to achieve a joint cavitation. (Beeton et al., 2010)

In some cases, mobilizations and TJM may lead to unintended Adverse Events (AE). Adverse Events following cervical mobilization or TJM, can be divided into minor or major AE.(Kranenburg et al., 2017a) Minor AE are more common following cervical physical manual therapy, and involve the onset of new symptoms or a temporary worsening of symptoms that last for 24 to 48 hours. Major AE following cervical treatments, and especially cervical TJM, have been described anecdotally, but are frequently discussed due to their serious clinical consequences such as spinal cord injury or stroke.(Hutting et al., 2018; Nielsen et al., 2017; Swait and Finch, 2017) Although TJM has been described as a risk factor for major AE, causality have not been proven. Incidence rates for major AE following TJM vary between 1 to 20.000 and 1 to 5,7 million TJM. (Assendelft et al., 1996; Haldeman et al., 2002; Nielsen et al., 2017) Minor AE are described more often and fluctuate from 23% up to 83% after a treatment session.(Chaibi et al., 2017; Rajendran et al., 2015) The large variation of incidence rates is challenging when discussing the 'risk-benefit ratio' during a shared decision making process.(Rushton et al., 2014) Moreover, the unpredictability of the risk of AE following cervical treatment, might make clinicians doubtful and unconfident when choosing techniques or performing cervical physical manual therapy. Although all Dutch Manual Physical Therapy programmes are fulfilling the International Federation of Orthopaedic Manipulative Therapists (IFOMPT)

educational standards, there are differences in educational programmes worldwide. (Thoomes-de Graaf et al., 2017) This might also contribute to the explanation of the difference in numbers of AE and might limit the generalizability of results worldwide. Factors which are influencing the occurrence of AE are not completely understood but can be divided into patients' related factors and clinicians related factors. Patient related factors are age, gender, history of smoking, and recent neck trauma.(Debette, 2014; Rushton et al., 2014; Thomas, 2016) Clinicians' related factors are work experience, level of education, educational programme, and applied treatment techniques. Knowing patients' and clinicians' characteristics and the type and frequency of treatment could be helpful in understanding risk factors for AE following cervical mobilizations and joint thrust manipulations.

The primary purpose of reporting AE is to learn from experience and monitoring progress in the prevention of errors. In the Netherlands, it is obligatory for clinicians to report all major AE to the Health and Youth Care Inspectorate and are also strongly advised report to their professional association. However, underreporting may be the case.(Kranenburg et al., 2017b; Leape, 2002) This may due to time pressure, fear of punishment, shame, fear of liability, loss of reputation and pear disapproval. (Leape, 2002; Mick et al., 2007) Thereby, if symptoms not immediately occur after treatment, clinicians could be unaware of the occurrence of AE.

Although TJM seem to be less often applied in the upper cervical spine than in the mid and lower cervical spine, the frequency of applied TJM in the Netherlands is currently unknown. Therefore, calculating the incidence of AE following cervical mobilizations and joint thrust manipulations in The Netherlands is not possible. The first step towards reduction the risk of the occurrence of AEs following CSM, is to understand its magnitude and determinants. Therefore, the objective of this study is to determine the number, type and predictors of AE following cervical treatments performed by Dutch manipulative clinicians.

METHOD

STUDY DESIGN AND SETTING

A prospective cohort study was performed in The Netherlands. Data were collected from September 2016 to September 2017. The Medical Ethical Committee of the University Medical Center Groningen, The Netherlands, deemed this study exempt and approved a waiver.

PARTICIPANTS

Potential participants were manual physical therapists, chiropractors, osteopaths and manual practitioners working in a primary care setting. Manual therapists were required to be graduated by an IFOMPT recognized university. Other professionals had to be recognized by their own national professional association. Recruitment was done using newsletters of professional associations (national and regional), alumni networks, snowballing, and by online recruiting on social networks.

To enhance compliance, the reporting system as to be used in this study, was based on the following criteria: 1] non-punitive, 2] confidential, 3] independent, 4] systems orientated, 5] simple to use, 6] voluntary and 7] has clear definitions. Additionally, related to compliance, participants could attend to a free conference before the study started. During this conference, participants received state of art information on the topic of adverse events after CSM. Also, participants received practical information and instructions about the study. The conference was recorded and published in an online environment which was only be available for participants.

CLINICIAN, PATIENT AND TREATMENT CHARACTERISTICS

Characteristics of the clinicians (profession, years of working experience and level and type of education) were registered. Every three months participants provided general clinical information and patient information during a day they chose as a representative average workday for them. The number of CSM applied on that day, the number of cervical patients treated with TJM that day, as well as demographic information of the patients who received TJM, and all minor AE were registered.

ADVERSE EVENTS

Participants were asked to define and classify adverse events according the classification by Kranenburg et. al.(Kranenburg et al., 2017a)

MAJOR ADVERSE EVENTS

When a major AE occurred, the clinician was asked to -anonymously- report the major AE and specific information regarding the patient and the treatment. Reporting could be done using a code which could trace back to the reporting profession but not to the clinician. A major AE had to be reported when it: 1] complied to the definition of a major AE and 2] the first symptoms started within four weeks after the CSM was applied. Additionally, to collect data on a national scale the Health and Youth Care Inspectorate and the professional associations were asked for major AE reports during that period.

MINOR ADVERSE EVENTS

Every three months clinicians were reporting patient and treatment information about all their cervical patients for a full working day. Clinicians could choose any day within a period of two weeks they felt was most representable for their average working day. During that registration day, all minor AE were inventoried from the last treatment and the treatment session itself.

DATA ANALYSES

Descriptive techniques were used to characterize the sampled data. Incidence was estimated by dividing the total number of new reported major AE by the total registered CSM applied. The number of AE over the total number of sessions was taken as outcome for binominal generalized linear models with the logit link using the explanatory variables for: 1] patient characteristics; 2] clinician characteristics, 3] treatment characteristics, and 4] AE characteristics. When a logistic analysis yielded influential data points according to Cook's distance or testing of studentized residuals, the analyses was replaced by robust binominal regression was applied using the statistical programming language R, version 3.5.3. (Cantoni and Ronchetti, 2001; R Core Team, 2019). Throughout the significance was set at .05.

PRIVACY MONITORING BOARD (PMB)

An independent supervisory board (PMB) was founded for this study in order to guarantee participants and patients their privacy when reporting a major AE. Also, the PMB could be contacted by participants when questions arose, and they did not wish to contact the research group. The PMB had two members which were executive board members of the two largest participating groups of clinicians (i.e. manual therapists and chiropractors) and was chaired by an independent non-clinician.

RESULTS

Of the 131 clinicians who signed up for the study, 55 clinicians (54 manual physical therapists and 1 chiropractor) delivered data of 392 patients. The remaining 76 clinicians did not send patient data, but did deliver their characteristics such as experience, age, gender and average working hours. The manual physical therapists reported data of 357 sessions. The chiropractor reported data on 35 sessions. Participating clinicians had a mean (SD) age of 38.8 (8.5) years with a mean (SD) working experience of 7.3 (6) years and 38 of them were male. On average, clinicians were seeing 3.5 patients each day during an average working week of 32.2 (SD6,9) hours. The 392 included patients had a mean (SD) age of 45.5 years (14.7) ranging

from 18-87 years; 251 were female. Most patients were treated with the indication neck pain (78.6%), restricted range of motion (42.6%), headache (34.9%), dizziness (6.6%) and 28.6% had another not further specified indication. Exercise was the most applied intervention (n=298), followed by mobilizations (n=249), and TJM (n=207) during all sessions. This resulted in an average of 0.99 TJM, 2.86 mobilizations and 1.76 exercises during one session.

ADVERSE EVENTS

Major AE were not reported by the participating clinicians in this study. Two cases of major AE were reported at The Health and Youth Care Inspectorate during that same period. One case of Major AE occurred during the treatment of a manual physical therapist and one case after a treatment by a chiropractor. Both cases were also reported to their own professional associations and were not included in our results.

Minor adverse events were reported in 28.1% of the treatment sessions. Minor AE that occurred were pain, muscle tenderness, aggravated headache, stiffness, fatigue, dizziness, radiation, radiation into the arm, a heavy arm, nausea, new headache, a thick throat, an uncomfortable feeling and puking. In sessions where only one intervention was applied TJM recorded the least minor AE with 6.1%, mobilizations scored 23.5% and exercises scored 44.3%. Sessions in which a TJM was applied, without additional mobilization, scored less minor AE (8.3%) than sessions in which a mobilization without additional manipulation was applied (29.4%). When analyzed per indication, the most minor AE were recorded for headache (40.1%), followed by a non-specified indication (28.8%), neck pain (27.9%), restricted cervical range of motion (25.1%) and dizziness (23.1%). Details for minor AE can be found in table 1.

Table 1. Indications, interventions and adverse events

Indication	***Patients(n)***	***Patients (%)***	***Ae (n)***	***Ae (%)***	***Pain (n)***	***Muscle tenderness (n)***	***Headache (n)***	***Stiffness (n)***	***Fatique (n)***	***Dizziness (n)***	***Radiation (n)***	***Radiation (n)arm***	***Heavy arm (n) (n)***	***Nausea (n)***	***Headche other (n)***	***Thick throat (n)***	***Unfomfortable feeling (n)***	***Puking (n)***
Neck pain	308	78,6	86	27,9	24	19	13	7	8	5	3	2	1	0	1	1	1	1
Rom	167	42,6	42	25,1	11	11	6	5	1	3	2	1	1	0	0	1	0	0
Headache	137	34,9	55	40,1	15	11	13	2	6	2	1	1	1	1	1	0	1	0
Dizziness	26	6,6	6	23,1	2	0	3	0	0	1	0	0	0	0	0	0	0	0
Other	111	28,3	32	28,8	9	8	1	5	4	0	2	2	1	0	0	0	0	0
All	392	100,0	110	28,1	31	24	15	10	10	6	4	3	2	1	1	1	1	1
Intervention																		
Only manipulation	33	8,4	2	6,1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Only mobilization	17	4,3	4	23,5	1	1	1	0	0	1	0	0	0	0	0	0	0	0
Only exercises	61	15,6	27	44,3	11	4	4	1	1	1	2	1	0	1	0	0	1	0

Table 1. Continued

Indication	*Patients(n)*	*Patients (%)*	*Ae (n)*	*Ae (%)*	*Pain (n)*	*Muscle tenderness (n)*	*Headache (n)*	*Stiffness (n)*	*Fatique (n)*	*Dizziness (n)*	*Radiation (n)*	*Radiation (n)arm*	*Heavy arm (n) (n)*	*Nausea (n)*	*Headche other (n)*	*Thick throat (n)*	*Unfomfortable feeling (n)*	*Puking (n)*
Man = y & mob = n	60	15,3	5	8,3	3	1	0	1	0	0	0	0	0	0	0	0	0	0
Man = n & mob = y	102	26,0	30	29,4	7	7	4	3	1	3	2	2	1	0	0	0	0	0
Man = y & mob = y	147	37,5	44	29,9	10	10	5	4	8	2	0	0	1	0	1	1	1	1

Abbreviations: Man = manipulation, mob = mobilization, exerc = exercises, y= yes, n = no

PREDICTORS

The indication headache (*P*= .0092) and gender of clinician (*P*= .0007) were considered a significant predictor for minor AE after a robust analysis. Other significant results from the classical univariate and multivariate logistic analysis were not confirmed by a robust analysis, not sensible to influential outlying cases in the data. Furthermore, all patient characteristic other than the indication headache (e.g. gender, age), all clinician characteristic (age, work experience and working hours per week) except for gender, or all different treatment techniques, resulted tested not significant by robust analyzes. Due to the relatively limited number of events, predictors could only be simultaneously analyzed by (robust) logistic regression aggregating over all AE's in the sense of taking a ``yes'' if any of the AE occurred.

Table 2a. Predictors for AE following manual therapy. Model 1: patient characteristics

	Estimate	***Std. Error***	***Z value***	***P value***	
Age	-0.0078	0.0090	-0.8688	0.3849	
Gender	-0.0185	0.2741	-0.0673	0.9463	
Indcation_Neck_Pain	-0.0014	0.3263	-0.0044	0.9965	
Indication_Headache	0.7310	0.2779	2.6303	0.0085	**
Indication_Dizziness	0.0459	0.5103	0.0900	0.9283	
Indication_ROM	0.0132	0.2634	0.0501	0.9600	
Indication_Other	0.1674	0.3246	0.5158	0.6060	

* = P≤ 0.05; **= P ≤ 0.01; ***= P ≤ 0.001

Table 2b. Predictors for AE following manual therapy. Model 2: patient and clinician characteristics

	Estimate	***Std. Error***	***Z value***	***P value***	
Age	-0.0089	0.0091	-0.9772	0.3285	
Gender	-0.0999	0.2840	-0.3519	0.7249	
Indcation_Neck_Pain	0.1559	0.3389	0.4599	0.6456	
Indication_Headache	0.7478	0.2887	2.5905	0.0096	*
Indication_Dizziness	-0.0125	0.5228	-0.0240	0.9809	
Indication_ROM	0.1200	0.2744	0.4375	0.6617	
Indication_Other	0.2529	0.3342	0.7984	0.4246	
Gender_clinician (female = 1)	0.2669	0.2679	3.4263	0.0006	**
Working_experience_ clinician	-0.0226	0.0240	-0.9399	0.3473	

* = P≤ 0.05; **= P ≤ 0.01; ***= P ≤ 0.001

Table 2c. Predictors for AE following manual therapy. Model 3: patient, clinician and treatment characteristics

	Estimate	*Std. Error*	*Z value*	*P value*	
Age	-0.0089	0.0096	-0.9270	0.3539	
Gender	-0.0917	0.2883	-0.3182	0.7503	
Indcation_Neck_Pain	0.1479	0.3419	0.4325	0.6654	
Indication_Headache	0.7780	0.2987	2.6041	0.0092	**
Indication_Dizziness	0.0870	0.5340	0.1629	0.8706	
Indication_ROM	0.0747	0.2783	0.2684	0.7884	
Indication_Other	0.2529	0.3401	0.7436	0.4571	
Gender_clinician (female = 1)	0.9153	0.2706	3.3829	0.0007	***
Working_experience_clinician	-0.0228	0.0244	-0.9323	0.3512	
Intervention_Manipulations_ session	0.0812	0.1066	0.7621	0.4460	
Intervention_Mobizations_ session	0.0194	0.0261	0.7415	0.4584	
Intervention_Exercises	0.0133	0.0780	-0.1703	0.8648	

* = P≤ 0.05; **= P ≤ 0.01; ***= P ≤ 0.001

DISCUSSION

The aim of this study was to determine the number, type and predictors of AE following cervical treatments performed by Dutch manipulative clinicians. There were no major AE in our sample. Due to the low incidence, our study group was too small to reliably determine the incidence of major AE. The incidence of minor AE following a treatment session was 28%. Minor AE that occurred were pain, muscle tenderness, aggravated headache, stiffness, fatigue, dizziness, radiation, radiation into the arm, a heavy arm, nausea, new headache, a thick throat, an uncomfortable feeling and puking. Only the indication headache and the gender of the clinician appeared significant predictors for a minor AE. Other indications, work experience of the clinician or interventions gave no significant predictors for minor AE.

Since no major AE was reported, incidence of major AE could not be calculated based on our sample. Furthermore, the number of cervical TJMs per session in our study seemed a little higher (0.99 vs 0.77) when compared to the study of Cagnie e.a. (Cagnie et al., 2004) This number is an essential part of the formula to calculate the incidence estimations. Furthermore, the average manual physical therapist in our study was seeing 3.5 cervical patients per working day, performed 0.99 manipulations per patient session, worked 4 days a week, and works 46

weeks per year. Also, in October 2018 approximately 4500 manual physical therapists were registered in The Netherlands.(Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF), 2018) Therefore, the estimated number of cervical manipulations per year in The Netherlands is: 3.5 sessions * 0.99 manipulations *4 days *46 weeks * 4500 therapists = 2.869.020 manipulations. However, one case was registered by the Health and Youth Care Inspectorate by manual physical therapist that year. Therefore, the incidence for major AE following TJM in The Netherlands is estimated at 1 per 2.869.020 cervical TJMs. Although the causality of major AE following cervical TJM is still debatable, an association has been described.(Church et al., 2016; Hutting et al., 2018; Nielsen et al., 2017) However, the heterogeneity of terminology in literature, the lack of an uniform reporting system and possible underreporting, makes the accuracy of these estimates debatable.(Gorrell et al., 2016; Kranenburg et al., 2017a) Moreover, these estimates should be seen together with the natural estimate to develop a dissection.(Hutting et al., 2018) Spontaneous dissections are estimated to have an annual incidence of 1.0-1.5 per 100.000 people for the vertebral artery and 2.3-3.0 per 100.000 people for the carotid artery. (Debette et al., 2009; Dziewas et al., 2003; Schievink et al., 1994)

Our finding that most AE following TJM are minor, and among these the most frequent reported are increased pain, tenderness, stiffness and headache, fatigue and dizziness and radiation, which is consistent with the literature.(Cagnie et al., 2004; Swait and Finch, 2017) The percentage of reported minor AE (28.1%) falls in the lower quartile when compared with other studies where occurrence percentages of 23-83% have been reported.(Chaibi et al., 2017; Rajendran et al., 2015) Senstad et al. suggested that during the first session more minor AE are reported.(Senstad et al., 1996) The cases in our sample were cervical patients on a random chosen workday. Therefore, it seems unlikely that most patients were included during their first session and might contribute to the lower percentage.

Headache seemed a predictor for minor AE, as seen in other studies. Specific therapeutic interventions such as TJMs were not or working experience. Contrary what one might expect was our finding that female clinicians seemed to be a predictor for minor AE as well. Our results therefore strengthen the impression that predictive factors for AE currently appear poorly understood due to inconsistent findings reported in the literature.(Swait and Finch, 2017) However, the comparisons of predictors should be interpreted with some caution since some studies surveyed the interventions to the whole spinal region instead of only the cervical region and

the possible influence of outlying observations is not explicitly ruled out.(Cagnie et al., 2004; Rajendran et al., 2015; Swait and Finch, 2017).

LIMITATIONS

Notation and interpretation of AE was done by the reporting therapists. Therefore, is it not possible to check whether the reporting clinician correctly interpreted and reported all AE's. To enhance clinician interpreting and uniformity of reporting and to in increase compliance, a symposium was organized at the start of the study and making it online available participants afterwards. Also, major AE could be reported anonymously. However, major AE could only be reported for their own profession. Unfortunately, not all manipulating professions were represented well in this study. Before the start of the study, all professional associations were contacted to inform them and to stimulate the participation of their members. Two professional associations were not interested in distributing information about this study and one professional association advised their members not to participate. The manual physical therapists appeared to be most dominant among 55 participants in total. Furthermore, the interventions during the treatment sessions were reported sufficiently explicit. However, elements outside the session (e.g. neck trauma, sports injuries or changes in work setting) which could have influenced the AE, were not reported. All results should therefore be interpreted with caution, within the perspective of this sample and might not be representable for other clinicians or settings.

STRENGTHS

The transparency and openness of the study was a major strength of this study. The independent privacy monitoring board with a delegation of different professional associations and an independent chair was valuable in gaining trust of the participants. Also, the web-based reporting system was user friendly and compatible for mobile devices as well. It fulfilled all our 7 predefined criteria, and therewith treatments could be reported accurate and fast. Furthermore, using advanced robust statistical methods results were corrected for outliers and repetitive testing. The self- selection of a representable workday every quarter for a therapist, should minimize selection bias and give a good insight in the treatment of a cervical patient. Therefore, it gives a better representation of an 'average' treatment session instead of the first session.

FUTURE RESEARCH

It is advisable to repeat these measurements about treatments for a longer period, on a regularly base and interdisciplinary supported by their professional associations. A larger sample measured over a longer period would give better insights and might familiarize clinicians with reporting systems. However, a reporting system should primarily have the purpose to gain insight, and therewith enhance prevention, and be based on a non-punitive character. Measuring should be performed uniformly, and worldwide so cultural and professional differences can be compared as well.

CONCLUSION

The incidence of major AE seems low. Based on the frequency of applied manipulations per session and the case reported at the Health and youth care inspectorate, major AE incidence following CSM is estimated at 1 per 2.869.020 cervical manipulations in The Netherlands. The incidence of minor AE is considerable with 28% and is more frequent in case of headache indication and female clinicians. However, there were no strong predictors indicated for minor AE.

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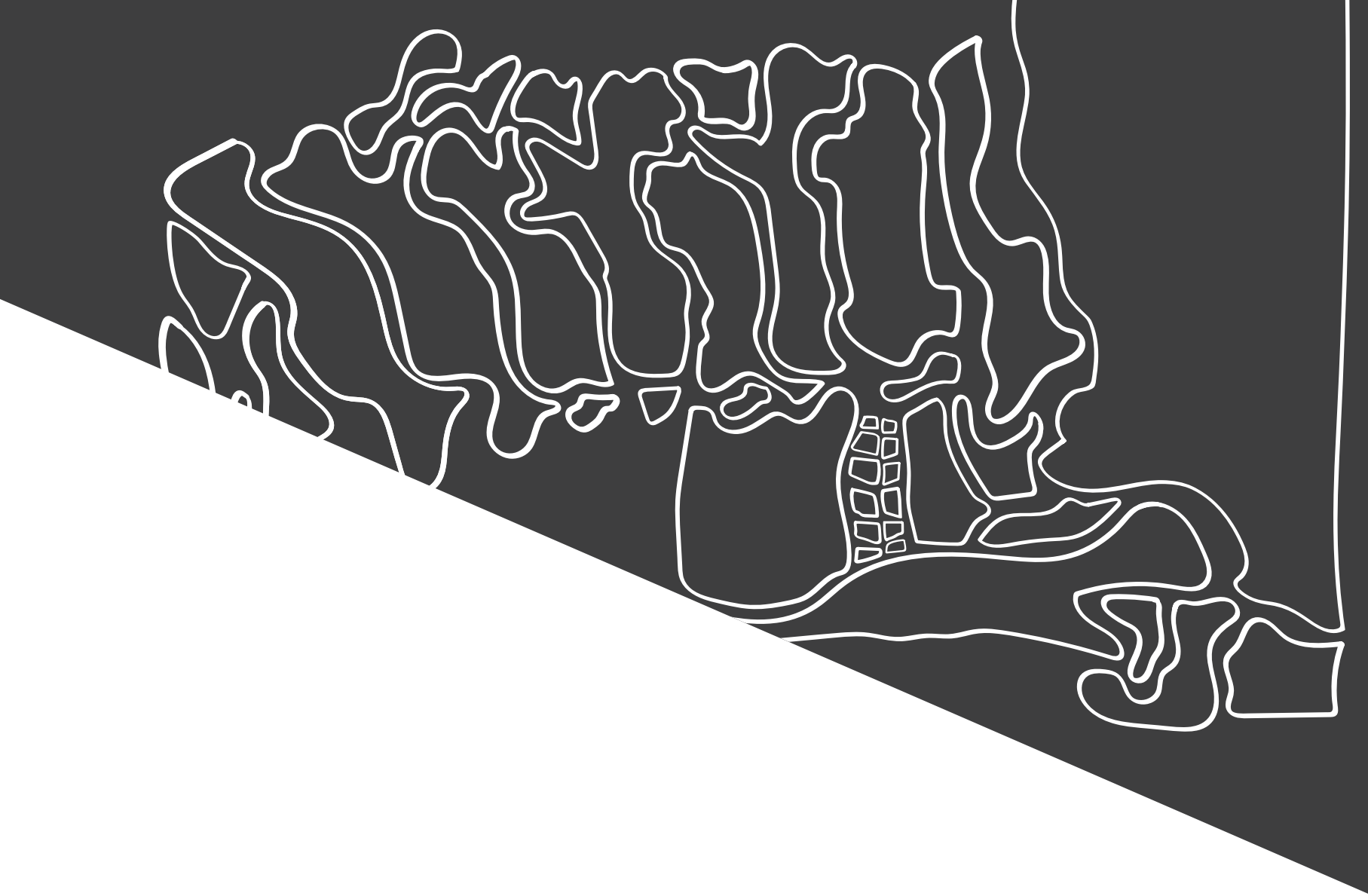

SUMMARY AND GENERAL DISCUSSION

8

SUMMARY

The aim of this PhD thesis was to get an insight into adverse events following manual physical therapy. The first study (**chapter two**) in this thesis describes a survey which showed that patients with cervical complaints are the largest group of patients in Manual Physical Therapists' out-patient clinics in The Netherlands. Furthermore, there is a significant difference in preferred treatment techniques between the upper cervical spine on one hand, and the mid/ lower cervical spine, thoracic spine and lumbar spine on the other hand. Clinicians indicated that, when comparing mid/ lower cervical spine, they use thrust manipulations with a high velocity and low amplitude less often in the upper cervical spine, they are less confident performing these upper cervical manipulations and feel that upper cervical manipulations are less safe than mid/ or lower cervical manipulations. The clinical experience of the therapist did not influence these results. This special status of the upper cervical spine might be amplified by the separate upper cervical professional standard in The Netherlands.

To obtain consensus on a classification system of adverse events after cervical manual physical therapy techniques, a Delphi study was performed (**Chapter 3**). Consensus was obtained amongst manual physical therapists, medical specialists and patients. The classified adverse events were linked to the International Classification of Diseases and Related Health Problems (ICD-10) and the International Classification of Functioning, Disability and Health (ICF).(World Health Organisation, 2012, 2001) The adverse events were classified in relation to severity (no, minor or major) and duration (hours, days, weeks). Mild to strong consensus was achieved on 29 of the 34 adverse events for all durations. For the remaining five adverse events, consensus was accomplished in two of three durations.

To gain insights in adverse events following cervical manipulations and mobilizations, a systematic review of case studies was performed (**chapter 4**). The review focused on characteristics of patients, clinicians and treatments in order to extract a patient profile for patients with an increased risk on major adverse events following cervical manual therapies. In most cases, major adverse events were associated with cervical manipulations and most patients were treated for the indication of neck pain. Furthermore, in 57% of the cases a cervical arterial dissection was reported and almost half of all patients had immediate symptoms following treatment. Unfortunately, characteristics of cases in de included studies were described poorly and therefore no clear patient profile, related to the risk of adverse events following cervical manipulations, could be extracted.

Although occurring sporadically, cervical arterial dissections seem the most described major adverse event following cervical manual physical therapy. With a case-control study (**Chapter 5**), it was attempted to identify risk factors for cervical arterial dissections following cervical manipulations. Cases of patients diagnosed with a cervical arterial dissection were retrospectively collected over three years (2014-2016) in the neurology department, neurosurgery department and the emergency department of the University Medical Center Groningen. Neck pain or headache patients receiving cervical manipulations in primary care were included as controls. Cases and controls were matched by gender and age. Firstly, the proportion of cases with a cervical manipulation in the period before the arterial dissection were identified. Secondly, differences in characteristics between cases and controls were analyzed. The risk factors for cervical arterial dissection as described by the International Federations of Orthopedic Manual Physical Therapists (IFOMPT) were used as a base.(Rushton et al., 2014) The proportion of patients with a cervical arterial dissection that received a manipulation prior to the arterial dissection is 4%. Cervical manipulations does not seem to be an important cause for arterial dissections. The comparison between the cases and the controls revealed no relevant risk factors. These results confirmed the difficulty clinicians in primary care experience when identifying patients with an increased risk for a cervical arterial dissection. Results also confirm that the IFOMPT framework is not sufficient to identify patient with an increased risk for a dissection after manual physical therapy.

To explore whether altering head and neck positions actually compromises cervical hemodynamic parameters, as literature suggests that this may be a risk factor in manual physical therapy, a systematic review was performed (**chapter 6**). It is hypothesized that mechanical stress on cervical arteries can cause a cervical arterial dissection particularly, in patients with pre-existent vascular pathologies. Therefore, insights in factors like potential changes of blood flow velocity or blood flow volume in varying positions and movements, might help to enhance diagnostic reasoning and the safety of interventions. The 31 included studies comprised data on 2254 participants. The combined data suggest that in the majority of people, most positions and movements of the cranio-cervical region do not have an effect on hemodynamic parameters. That means, in conclusion, that positions and movements of the cranio-cervical region are no risk factor related to adverse events following manual physical therapy.

A prospective cohort study (**chapter 7**) was performed over 12 months in The Netherlands to determine the number, type and predictors of adverse events following treatments by manipulative therapists. Factors related to patients, clinicians and the treatments were inventoried. Additionally, the Health and Youth Care Inspectorate and professional associations were asked to share reported adverse events. An independent privacy monitoring board was founded to supervise the ethical aspects of the data collection, i.e. privacy, in order to increase the participation on the study. Data were collected from 392 treatments. Clinicians averagely treated 3.5 cervical patients per day using 0.99 manipulations, 2.9 mobilizations and 1.8 exercises per treatment. Most reported adverse events were minor. No adverse events were reported in our sample. Two major adverse events were reported to the IGJ in that period. The incidence of major adverse events was estimated at 1:2.869.020 cervical manipulations. No strong predictors for adverse events could be determined.

GENERAL DISCUSSION

Manual physical therapy is considered as being effective for non-specific neck pain and neck related headache.(Bier et al., 2018; Blanpied et al., 2017; Gross et al., 2015; Moore et al., 2017) However, there is a debate in literature and amongst clinicians about the use of these therapeutic interventions in relation to the risk of complications following manual physical therapy. Within the process of clinical reasoning, clinicians should weigh the potential risks against the potential benefits. Up till now, there is lack of information about the frequency of occurrence and characteristics of adverse events following manual physical therapy (and comparable interventions) applied to the cervical spine. Insight in the numbers needed to treat and numbers needed to harm is, to our knowledge, missing.

The general aim of this thesis was to identify patients which are more at risk for adverse events following manual physical therapy by identifying and understanding risk factors within the patient, therapist and treatment techniques. Unfortunately, by using a systematic literature review and using prospective and retrospective cohort studies it was not possible to identify exclusive predictors for adverse events following cervical manipulations. The combination of the complexity and rarity of the adverse events made it challenging to achieve that purpose. Additionally, in the few cases in which a major adverse event was present, most clinical symptoms were overlapping the arterial and musculoskeletal domain. Therefore, it is good to realize that the tools to identify major adverse events are limited. Arterial tests seem invalid, and no strong characteristics in patients, clinicians or treatment techniques have been identified yet. Moreover, even the IFOMPT framework seems not able to differentiate between patients with complaints originating from the musculoskeletal and arterial system. This confirms the difficulty clinicians experience in practice to identify patients at risk. Although they present themselves scarcely, only the patients that present with very distinctly deviating symptoms can be identified in clinic. The majority of patient with a cervical arterial dissection can only be identified in a last stage of the process by severe neurological symptoms. However, it remains the duty of the clinician to keep trying to recognize those patients, while extremely difficult, as early as possible. Although risk factors and predictors are lacking and altered neck positions do not seem to increase mechanical stress to an arterial wall during treatments, clinicians should not leave a stone unturned as it comes to patient safety but keep being realistic at the same time. Due to low incidence of cervical arterial dissections and the high diagnostic costs, it is not realistic to do a Magnetic Resonance Angiography (MRA) for every patient who qualifies for cervical spinal manipulations. Especially, since causality has not been established.

In line with the scarce information available regarding the potential risks, little is known about the additional benefits of cervical manipulations over other interventions.(Gross et al., 2015) The added value over other (manual) techniques seems limited and raises the question why cervical manipulations should be performed at all. However, two point are easily overlooked in that essential debate that should be ongoing. Firstly, the fact that major adverse events are more often described in case reports following cervical manipulations (**chapter four**) could be the result of a publication bias. Simply, as the commonly occurring cavitation during the manipulation makes a manipulation is easier to identify during treatment than a mobilization. Especially in The Netherlands where you are obligated to sign an informed consent as a patient for all upper cervical manipulations. Additionally, the performed prospective study (**chapter 7**) showed no significant differences between manipulations, mobilization, exercises or a combination of the above mentioned for adverse events. Secondly, that little added value of an intervention in comparison to other interventions, such as a cervical manipulation vs mobilizations, has been described yet, doesn't mean the intervention should be abandoned when risks are utterly low. However, it does mean that all possible precautions should be taken to prevent adverse events. Therefore, it is still advised to be cautious with manipulative techniques in the cervical spine and only to use them after a solid patient history and when the symptoms seem reproducible from the musculoskeletal system. After such a sound diagnostic process and a correct execution of treatment techniques, a clinician remains responsible but cannot held liable.

Nevertheless, if an adverse event has occurred it will be traumatic for both, the patients and clinician, but should be reported. Preferably, this reporting should be done by the treating clinician for they probably have the most relevant details available. For example, details about the patient's history prior to the dissection as well as details about the given treatment and used techniques. The introduced classification system of adverse events should contribute to the clarification of the severity of an adverse event and simplify the reporting of it. However, it is also advised that the Health and Youth Care Inspectorate and professional associations focus on a reporting system that is focused primarily to gain insight in the process and therewith enhance prevention. Therefore, it might work best when such a system has a non-punitive character, guards against blaming and shaming, and supports the clinician. The clinician also might be considered a second victim, since it is also traumatic for the clinician. However, a clinician remains responsible for his/ her actions and should not be discharged from the obligation to report.

Whilst the causal relationship between the adverse events and the cervical manipulation regularly remains unclear, the incidence of major adverse events is low. Consequently, it is extra important to report all cases. Therefore, it might be time for professional associations take responsibility and initiate and facilitate an international, and preferably interprofessional, registry based on the before mentioned criteria.

METHODOLOGICAL CONSIDERATIONS

Unfortunately, the number of included participants in our survey, prospective study and case-control study were limited. When using the number of cervical manipulations (2.869.020) as estimated in the performed prospective cohort study (**chapter 7**) for a power calculation, a general confidence level of 80% and a margin of error of 5% results in a sample size of 164 people. However, given the sensitivity of the subject a confidence level of 95% might be more in place. Which would result in a desired sample size of 385 patients experiencing a major adverse event. Even though it was tried by all means it was therefore difficult to make firm statements on incidence or risk factors. This emphasizes the importance for clinicians to participate in such studies. Given the rarity of major adverse events high participation numbers of clinicians and patients are necessary. To organize studies including such large numbers of participants, an international collaboration is strongly advised. Therefore, it might be wise that an international professional association like IFOMPT initiates such a study which is and facilitated and led by national professional associations.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Most manual physical therapy treatments are without adverse events and cervical manipulations seem safe. Most adverse events are minor and major adverse events are scarce and causality remains frequently undecided. However, in clinical practice it remains difficult to identify patients at risk due to the low incidence and wide variation of presented symptoms. Well organized, larger studies with a longer duration that are supported and carried internationally might cut the mustard. And if such a system can be facilitated worldwide and interprofessionally, intercultural and interprofessional differences could be measured as well.

NEDERLANDSE SAMENVATTING

Manueel therapeutische behandelingen worden frequent toegepast bij patiënten met nek- en/of hoofdpijn. Naast oefeningen en advies over houding en beweging bestaan deze behandelingen uit mobiliserende of manipulatietechnieken. Mobiliserende technieken onderscheiden zich van manipulatietechnieken door een verschil in de snelheid waarmee de handeling wordt uitgevoerd en in de bewegingsuitslag. De snelheid waarmee de handeling wordt uitgevoerd bij een mobilisatie is aanzienlijk lager en de beweging vindt plaats over een groter traject dan bij een manipulatie. Zowel onder leken als onder zorgprofessionals bestaat de veronderstelling dat manueel therapeutische handelingen die worden toegepast aan de halswervelkolom (cervicale wervelkolom) kunnen leiden tot complicaties. Er is tot nu toe geen duidelijk causaal verband gevonden tussen de handelingen en ernstige complicaties. Bovendien wordt slechts sporadisch casuïstiek gepubliceerd met ernstige complicaties die tijdens of na manuele behandelingen van de halswervelkolom ontstaan zijn. De schattingen van het voorkomen van complicaties variëren enorm. Daarnaast is niet duidelijk welke patiënten een hoger of lager risico lopen op dergelijke complicaties. Meer duidelijkheid daarover is van belang voor zowel therapeut als patiënt.

Het doel van dit proefschrift was om meer inzicht te krijgen in aard en de omvang van potentiele complicaties na het toepassen van manueel therapeutische handelingen aan de cervicale wervelkolom bij mensen met nekpijn en/of hoofdpijn. De eerste studie (**hoofdstuk 2**) in dit proefschrift beschrijft dat het grootste aandeel van de patiënten die een manueel therapeut consulteert in een Nederlandse eerstelijns praktijk dat doet wegens klachten aan de halswervelkolom. Daarnaast wordt er door manueel therapeuten verschillend gedacht over het toepassen van behandeltechnieken in de hoog cervicale, mid/ laag cervicale, thoracale en lumbale wervelkolom. Therapeuten gaven aan dat ze, in vergelijking met mid/ en laag cervicaal, hoog cervicaal minder vaak manipulatietechnieken gebruiken omdat ze bang zijn voor het optreden van ernstige complicaties. Tevens gaven manueel therapeuten aan dat ze minder zelfverzekerd zijn bij het uitvoeren van manipulaties in de hoog cervicale regio ten opzichte van dezelfde technieken in de laag en mid cervicale regio. De klinische ervaring van de therapeut lijkt deze opvattingen niet te beïnvloeden. De speciale status die de hoog cervicale wervelkolom daarmee inneemt wordt wellicht versterkt doordat er een expliciete toestemmingsprocedure gevolgd moet worden voorafgaande aan een hoog cervicale manipulatie. Deze procedure bevat een voorlichting waarin de potentiele risico’s en baten besproken moeten worden en de patiënt bij voorkeur een handtekening zet op een informed

consentformulier. Deze procedure is manueel therapeuten opgelegd door de Nederlandse Vereniging voor Manuele Therapie.
Voor het melden van complicaties na manuele therapie is het belangrijk dat het duidelijk is wat er wordt verstaan onder een complicatie. Met andere woorden: welke potentiele symptomen volgend op cervicale manuele therapie worden er beschouwd als complicatie. Om tot een classificatiesysteem voor complicaties na cervicale manuele therapie te komen, waarover overeenstemming bestaat, is een Delphi-studie uitgevoerd (**hoofdstuk 3**). In een Delphi studie wordt in een aantal vragenrondes door experts, die voor elkaar anoniem zijn, geprobeerd een consensus te bereiken. Voor het bereiken van oversteenstemming over een classificatiesysteem voor complicaties na cervicale manuele therapie is aan een panel van 31 manueel therapeuten, medisch specialisten en patiënten gevraagd deel te nemen aan het onderzoek. De Delphi-studie leidde tot de volgende resultaten: de potentiele complicaties zijn gekoppeld aan de Internationale Classificatie van Ziekten en Gezondheid gerelateerde problemen (ICD-10) en de Internationale Classificatie van Functie, beperking en gezondheid (ICF). De complicaties zijn ingedeeld naar ernst (geen, licht en zwaar) en duur (uren, dagen en weken). Milde tot sterke overeenstemming is behaald in 29 van de 34 complicaties (zoals bijvoorbeeld: overgeven, pijn, CVA en overlijden) voor alle tijdseenheden (uren, dagen en weken). Voor de overige vijf complicaties (depressie, gewrichtspijn, paniek aanvallen, draaiduizeligheid en visuele verstoringen) werd consensus bereikt in twee van de drie tijdseenheden.

Om een inzicht te krijgen in de aard van de complicaties na cervicale manipulaties is na een systematische beoordeling en analyse een overzicht van casusstudies uitgevoerd (**hoofdstuk 4**). Dit overzicht concentreerde zich, naast de aard van de beschreven complicaties, op karakteristieken van patiënten, behandelaren en behandelingen met als doel om een patiëntprofiel of patiënten met een hoger risico op complicaties na cervicale manuele therapie te identificeren. In de meeste casussen werden ernstige complicaties geassocieerd met cervicale manipulaties. De meeste patiënten werden behandeld voor nekpijn. In 57% van de casussen werd een scheur van de halsslagader (dissectie) gerapporteerd en van die patiënten ervoer bijna de helft direct na de handeling de eerste symptomen. De karakteristieken waren in de meeste geïncludeerde artikelen matig beschreven. Daarom kon er geen profiel geëxtraheerd worden van patiënten die een vergroot risico lopen op ernstige complicaties na cervicale manuele manipulaties.

Een scheur van de halsslagader komt zelden voor na cervicale manipulaties, maar lijkt wel de meest beschreven ernstige complicatie te zijn. Middels een case-control studie, een studie waarin karakteristieken van patiënten met een scheur in de halsslagader (cases) vergeleken worden met karakteristieken van patiënten die cervicale manipulatie ondergaan (controls) en waarbij er geen complicaties optraden, (**hoofdstuk 5**). In deze studie is geprobeerd risicofactoren voor een scheur van de halsslagader na cervicale manipulatie te inventariseren. Informatie van patiënten met een scheur van de halsslagader is verzameld over een periode van 3 jaar (2014-2016) op de afdelingen neurologie, neurochirurgie en de spoedeisende hulp van het Universitair Medisch Centrum Groningen. Patiënten met nekpijn en hoofdpijn die cervicale manipulaties ondergingen in een regulier behandeltraject werden geïncludeerd als controlegroep. Cases en controls werden 1-op-1 gekoppeld op basis van geslacht en leeftijd. Allereerst werd de groep met cases met een recente cervicale manipulatie in de periode voorafgaande aan de scheur van de halsslagader onderzocht. Vervolgens zijn de verschillen in karakteristieken tussen de cases en de controls geanalyseerd. De risicofactoren voor inscheuring van de halsslagader, zoals beschreven door de International Federation of Orthopedic Manual Therapists (IFOMPT), werden gebruikt als referentie. (Rushton et al., 2014) Slechts 4% (n=2) van de patiënten met een scheur van de halsslagader had een recente cervicale manipulatie ondergaan. Cervicale manipulaties lijken een zeer beperkte rol te spelen bij het ontstaan van een scheur van de halsslagader. De analyses van de karakteristieken van de cases en de controls lieten geen relevante risicofactoren zien. Deze resultaten bevestigen dat het moeilijk is om de patiënten met een verhoogd risico op cervicale dissectie te identificeren. De resultaten laten ook zien dat het IFOMPT framework niet afdoende is om patiënten met een verhoogd risico op inscheuring van de halsslagader na cervicale manipulaties te identificeren.

Er wordt in de literatuur verondersteld dat mechanische stress op de wand van een slagader, in het bijzonder inscheuring van de halsslagader, kan veroorzaken. Inzicht in de veranderingen van bloeddoorstromingssnelheid en doorstromingsvolume bij positieveranderingen van de halswervelkolom kunnen van waarde zijn bij het klinisch redeneren en de te kiezen behandeltechniek. Er werd een systematisch literatuuronderzoek uitgevoerd om te onderzoeken of hier aanwijzingen voor zijn (**hoofdstuk 6**). De 31 studies die geïncludeerd zijn bevatten de gegevens van 2254 deelnemers. De gecombineerde resultaten suggereren dat de meeste positieveranderingen in de halswervelkolom niet van invloed zijn op de bloedstrooming. Concluderend kan daarmee gesteld worden dat veranderingen

van positie van de halswervelkolom tijdens het uitvoeren van een behandeling geen risicofactor lijkt zijn bij inscheuring van de halsslagader na cervicale manipulaties.

In **hoofdstuk 7** is gedurende 12 maanden in Nederland een prospectieve cohortstudie uitgevoerd. Het doel van deze studie was het aantal, het type en voorspellers van complicaties na cervicale manipulaties vast te stellen. Gegevens van 392 behandelingen zijn verzameld. Behandelaren rapporteerden gemiddeld 3,5 cervicale behandelingen per dag. Daarbij gebruikten ze per behandeling gemiddeld 0,99 manipulaties, 2,9 mobilisaties en 1,8 oefeningen. De meeste gerapporteerde complicaties waren licht van aard. In onze verzamelde data werden geen ernstige complicaties gemeld. Aanvullend op de prospectieve cohortstudie zijn meldingen van complicatie na manueel therapeutische behandelingen bij de Inspectie Gezondheidszorg en Jeugd (IGJ) en de beroepsverenigingen van manueel therapeuten en chiropractors opgevraagd. De IGJ rapporteerde twee ernstige complicaties in dezelfde 12 maanden waarin de prospectieve studie werd uitgevoerd. Op grond van de gevonden gegevens wordt de incidentie van ernstige complicaties geschat op 1 op 2.869.020 cervicale manipulaties. Er zijn geen sterke voorspellers voor ernstige complicaties gevonden.

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