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ORIGINAL RESEARCH

Identifying Patient Characteristics Associated With the Occurrence of Post Treatment Non-serious Adverse Events After Cervical Spine Manual Therapy Treatment in Patients With Neck Pain

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Abstract

Objectives: To compare prevalence rates of serious and non-serious adverse events after manipulation and mobilization and to identify risk factors of serious and non-serious adverse events following 4 types of manual therapy treatment in patients with neck pain.

Design: A prospective cohort study in primary care manual therapy practice.

Participants: Patients with neck pain (N=686) provided data on adverse events after 1014 manipulation treatments, 829 mobilization treatments, 437 combined manipulation and mobilization treatments, and 891 treatments consisting of "other treatment modality".

Interventions: Usual care manual therapy.

Main Outcome Measures: A chi-square test was performed to explore differences in prevalence rates. Logistic regression analysis was performed within the 4 treatment groups. A priori we defined associations between patient-characteristics and adverse events of odds ratio (OR)>2 or OR<0.5 as clinically relevant.

Results: No serious adverse events, such as cervical artery dissection or stroke, were reported. With regard to non-serious adverse events, we found that these are common after manual therapy treatment: prevalence rates are ranging from 0.3% to 64.7%. We found a statistically significant difference between the 4 types of treatments, detrimental to mobilization treatment. Logistic regression analysis resulted in 3 main predictors related to non-serious adverse events after manual therapy treatment: smoking (OR ranges from 2.10 [95% confidence interval [CI] 1.37-3.11] to 3.33 [95% CI 1.83-5.93]), the presence of comorbidity (OR ranges from 2.32 [95% CI 1.22-4.44] to 3.88 [95% CI 1.62-9.26]), and female sex (OR ranges from 0.22 [95% CI 0.11-0.46] to 0.49 [95% CI 0.28-0.86]).

Conclusion: There is a significant difference in the occurrence of non-serious adverse events after mobilization compared with manipulation or a combination of manipulation and mobilization. Non-serious adverse events in manual therapy practice are common and are associated with smoking and the presence of comorbidity. In addition, women are more likely to report non-serious adverse events.

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The study was approved by the medical ethics committee of Erasmus MC, Rotterdam, The Netherlands, under registration number MEC-2007-359.

Disclosures: none.

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Cervical spine manipulation and cervical spine mobilization are commonly used (treatment) modalities for the treatment of patients with neck pain. An Australian survey among manipulative therapists shows that cervical spine manipulative techniques are used by 84.5% of manipulative therapists in patients with neck pain.[1] Six to 12% of the population with neck pain undergoes cervical spine manipulation annually.[2] Manual therapy (MT) is beneficial to patients with neck pain,[3,4,5] especially when used in combination with exercise.[5] MT in The Netherlands may consist of high velocity thrust (HVT) manipulation or low velocity non-thrust mobilization, but also exercise to stabilize the spine and other modalities. Despite evidence to support the benefits of cervical HVT manipulation, the use of this treatment modality still remains controversial because of its potential risks of serious adverse events (AEs).[6,7,8] AEs after interventions to the cervical spine are commonly divided into 2 groups: serious and non-serious. There is no clear consensus concerning the definition of both serious[9,10,11] and non- serious AE.[6,12,13] But, commonly, serious AE refer to events resulting in life-threatening situations or even in death, while the non-serious AE are benign in nature and of short duration (resolve within 24 h) non-serious AEs can then be further divided into common and uncommon reactions based upon the frequency of their occurrence.[6,14] Fortunately, the occurrence of serious AE (such as cervical artery dissection, stroke, or transient ischemic attack) after cervical spinal manipulation is rare.[13,15] Incidence rates range from 1 in 100,000 to 1 in several million.[16] There is, however, evidence to suggest that the reporting of AE is too poor and incomplete to enable any meaningful interpretation of risk.[13,17,18,19]

Serious AEs were considered to be primarily—and often even exclusively—related to manipulation techniques.[20] Reported risk factors for serious AE include age, biological sex, hypertension, diabetes, migraines, use of oral contraceptives, and smoking.[21,22,23] For non-serious AEs, no other risk factors besides having experienced >60 days of neck pain in the preceding year (which may predict new or increased headache after spinal manipulation) are identified.[24] So, in the absence of identified risk factors for non-serious AEs, how are we able to properly inform the patient about the risk? And, MT as applied in daily clinical practice rarely consists of HVT manipulation as a single modality, but rather tends to consist of a combination of interventions. With non-serious AE being common, it is hypothesized that AE events are not exclusively related to cervical manipulative thrust techniques.

A treatment modality approach is needed in order to assess the occurrence of AE in MT interventions as applied in usual care manual therapy treatment and to accurately assess treatment modalities in relation to the occurrence of AE.

The main aim of the current study is to gain insight in the occurrence of serious and non-serious AEs after MT treatment in patients with neck pain. Secondly, we want to explore the risk factors of non-serious AEs after spinal HVT manipulation and non-thrust mobilization in patients with neck pain.

List of abbreviations:

AE	**adverse event**
CI	**confidence interval**
FABQ	**Fear Avoidance Beliefs Questionnaire**
GPE	**global perceived effect**
HVT	**high velocity thrust**
MOB	**mobilization**
MP	**manipulation**
MT	**manual therapy**
NBQ	**Neck Bournemouth Questionnaire**
NDI	**Neck Disability Index**
NRS	**Numeric Rating Scale for pain**
OR	**odds ratio**

Methods and materials

Design

A prospective multicenter inception cohort study with a 12-month follow-up period in a Dutch manual therapy setting.

Subjects

Manual therapists

All manual therapists participating in this study were licensed and registered. Participating manual therapists studied manual therapy for 3 or 4 years and hold a Master's degree in Manual therapy. Prior to the current study, all participants followed a 2-day course on the study protocol.

Patients

Patients entering the manual therapy practice with nonspecific neck pain, aged between 18 and 80 years and able to read and write Dutch were eligible for participation. Neck pain was defined as pain in the area between the occiput and the spine of scapulae.[25] Patients with known specific causes of neck pain (eg, known vascular or neurologic disorders, neoplasms, rheumatic conditions) were excluded. All patients received information on the study and signed an informed consent form. The study was approved by the medical ethics committee of Erasmus MC, Rotterdam, the Netherlands.

Procedures

Patient characteristics and clinical characteristics were registered by the MT on a website provided by the researchers. After registration, a unique code was assigned to each patient in order to combine treatment and AE data. Participating patients signed informed consent. Patients were screened for eligibility using the a priori defined criteria.

Manual therapists

Within a 3-month inclusion period, each manual therapist was asked to include 5 consecutive patients with non-specific neck pain. Manual therapists were instructed to provide usual care MT.

The cervical spine was defined as the region between C0 and C6, whereas treatment on C7-T1 and treatment in the thoracic spine was excluded for analysis. Treatment modality, date, and number of sessions, as well as the process of clinical reasoning were registered by the therapists. Treatment modalities were a priori divided into 4 groups: HVT manipulation, non-thrust mobilization, a combination of HVT manipulation and non-thrust mobilization, and a group of other modalities. When a patient was manipulated within a treatment session, this session was defined as a manipulation (MP) session. When a patient received a mobilization technique, this session was defined as a mobilization

(MOB) session (by the absence of manipulation). When the patient was treated with both manipulation and mobilization within 1 session, this was defined as MP+MOB session. Treatment sessions in which the patient received techniques other than manipulation or mobilization were defined as "other". Besides these a priori categorized modalities, other modalities within the definition of "usual care" for patients with neck pain, like information, advice, or exercise can be provided.

Patients

Patients were asked to provide information on possible risk factors for AE. Reported risk factors for serious AE include age, biological sex, smoking, and presence of comorbidity (hypertension, [history of] heart failure, diabetes mellitus, hypercholesterolemia, atherosclerosis, and migraine).[21,22,23]

At baseline, patients' health status was surveyed using questionnaires on functioning, disability, and related factors, like psychological factors. Disability was measured using Neck Disability Index (NDI, range 0-50). Psychological factors included anxiety, depression, fear for (re)injury and activity related pain. Anxiety and depression were identified by the mean score of the anxiety and the depression questions of the Neck Bournemouth Questionnaire (NBQ, range 0-10). Avoidance of physical activities was measured with the the Fear Avoidance Beliefs Questionnaire-Physical Activity subscale (FABQ-PA, range 0-24).

Additionally, based on the literature, a number of prognostic factors were measured: pain intensity (by means of a numeric rating scale for pain [NRS, range 1-10]), duration of neck pain, recurrence of neck pain, marital status, work status, sports engagement, and the presence of concomitant symptoms (eg, low back pain).

The clinical reasoning and applied interventions were registered by the manual therapists. Patients reported on AE using the Adverse Events Questionnaire, which was filled out by the patient within 48 hours after each treatment. The Adverse Events Questionnaire asks if the patient experienced any unpleasant reaction after treatment, and requests to report the type of reaction, time of onset (range 1-4), duration (range 1-4), and intensity of symptoms (range 1-10). The questionnaire has been used before[6,8,21] and consists of several potential/possible post treatment reactions. Patients had the option to add reactions to the questionnaire that were not mentioned in the questionnaire.

At the end of the treatment episode, patients filled out the NRS, NDI, NBQ, and FABQ again. Additionally, the Global Perceived Effect (GPE) questionnaire was filled out by the patients). The GPE is scored on a 7-point Likert scale ranging from "total recovery" to "worse than ever". Test-retest reliability of GPE is excellent.[26] All questionnaires were returned to the researchers in a prestamped envelope. Design and timeline of the study are presented in figure 1.

Data analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software (version 24.0). Four types of treatment modalities were defined (MP, MOB, MP+MOB, and other). Each type of treatment modality was analyzed separately for the risk of occurrence of AE. Additionally, patient characteristics were included in order to assess the influence of these patient characteristics on the relation between treatment modality and AE.

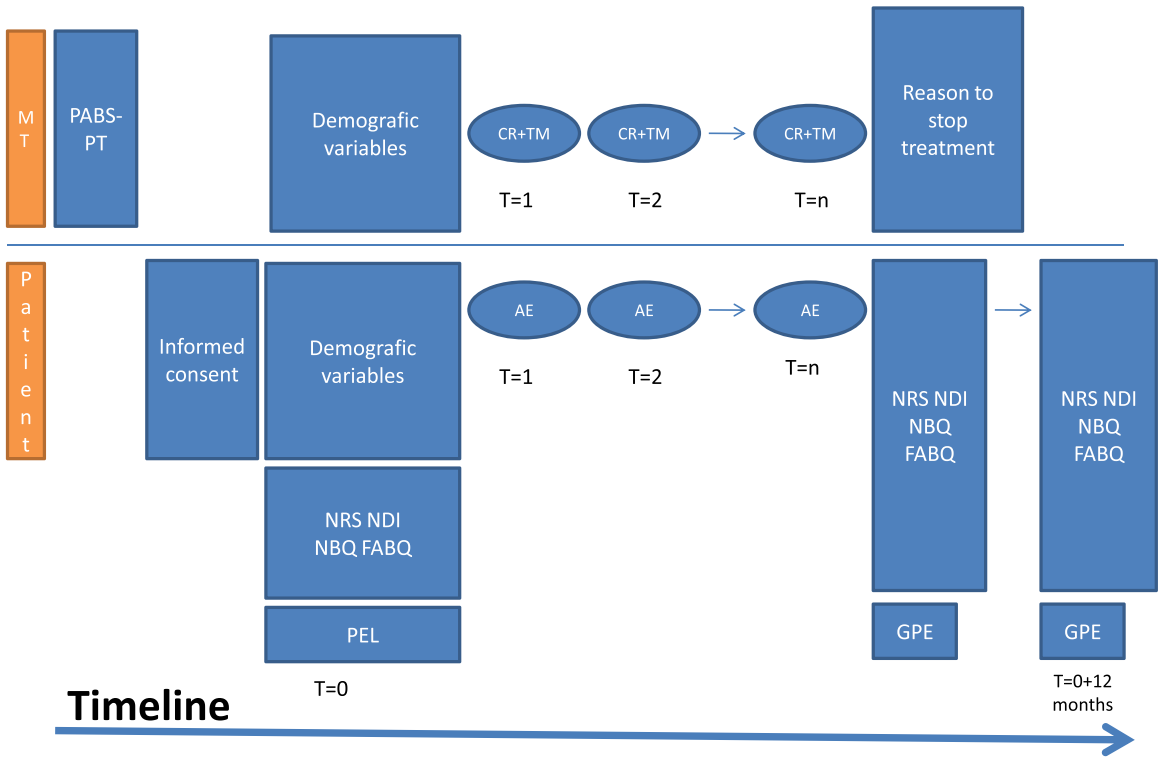

Fig 1 Timeline and design of the study. CR, clinical reasoning; TM, treatment modalities; T=0+n, end of treatment episode; T=0+12 months, follow-up.

Descriptive statistics (frequencies, mean, standard deviation, and range) were calculated for AE within each treatment group.

Descriptives

For all participating manual therapists, frequencies, mean, and standard deviation were calculated for age, years of work experience, weekly hours of work, and weekly number of patients with neck pain. Distribution of biological sex was registered.

For all participating patients, frequencies for age, biological sex, duration of complaints, recurrence of complaints, direct access or referral by general practitioner or medical specialist, smoking, marital status, work status, sport engagement, and presence of concomitant symptoms were calculated.

Within the treatment groups, frequencies of possible risk factors (age, biological sex, smoking, presence of comorbidity, pain intensity, disability, fear avoidance, and anxiety and depression) were calculated.

Regression analysis

Direct logistic regression analysis was performed to assess the effect of a number of factors on the likelihood that patients would experience an AE after manual therapy treatment. In order to grade AE, we decided that the occurrence of cramps, dizziness, blurred vision, nausea, tinnitus, vomiting, vertigo, and weakness of the limbs are undesirable and uncommon and the occurrence (intensity >1) can be defined as non-serious AE. For the commonly occurring headache, stiffness, aggravation of complaints, radiating pain, and fatigue, the intensity should be >5 and the duration longer than 24 h to be defined as a non-serious AE (figure 2). To prevent overfitting, the number of preselected predictors was chosen taking into account the 1:10 rule.[27] In order to check for multicollinearity, Pearson's correlation coefficients were calculated. In the case of significant correlation, regression analysis was performed with only 1 factor at a time. Factors were entered into logistic regression models for the different treatment groups (MP, MOB, MP+MOB, and "other modalities"). To describe possible risk factors of AE after manual therapy treatment, the following dichotomous independent variables were included into the model: biological sex, smoking, and presence of comorbidity. Continuous independent variables put into the model were age, pain intensity, disability, anxiety and depression, and fear avoidance. Occurrence of non-serious AE was included into the model as a dichotomous dependent variable.

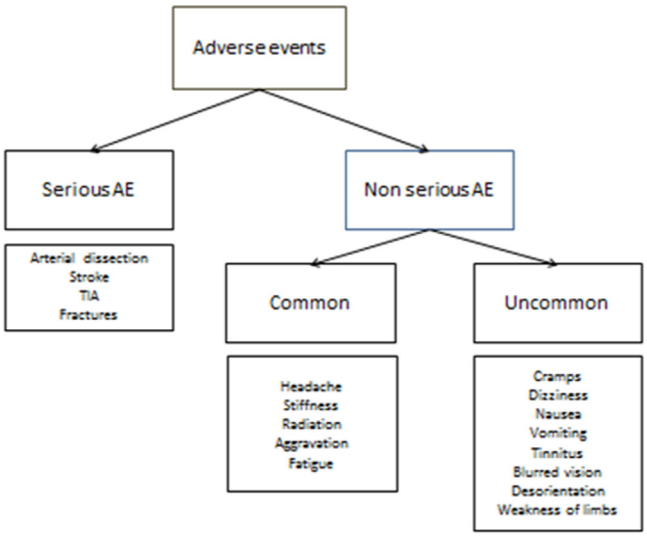

Fig 2 Timeline and design of the study. TIA, transient ischemic attack.

Results

Description of the study sample

Manual therapists

Of the 287 manual therapists eligible to participate, 263 joined the study. Reasons for non-participation (n=24) were pregnancy (n=2), working in a rehabilitation center (n=2), working in a foreign country (n=2), study delay/missed study deadline (n=16), and stopped studying (n=2). Most participating manual therapists were male, aged ≥40 years, with about 20 years of working experience. The average number of included patients per MT was 5. MT characteristics are presented in table 1.

Patients

During the recruitment period, 3813 patients were eligible for participation; of these 1195 were included and 2618 were not. Main reasons for non-enrolment were that the MT already included the maximum of 5 consecutive patients, or patients were not willing to participate. 57.4% complete cases (consisting of both patient and manual therapist data) were received, resulting in 686 patients to be analyzed. Participants were predominantly female (69.4%) and 44.7% suffered from neck pain ≥12 weeks, mostly recurrent. Most patients had 1 or more concomitant complaints. Participants had an average age (SD) of 46.4 (13.6) years. Average pain score (SD) was 4.9 (2.1) on NRS (range 1-10). Mean disability measured on NDI (range 0-50) was 22.7 (6.4), and fear avoidance measured on FABQ (range 0-96) was 10. Anxiety and depression measured on NBQ (range 0-20) was 4.1 (2.3). Almost 1 in 4 patients were smokers (23.6%). In 11.4% of patients, comorbidity, in most cases hypertension (4.1%) and (history of) heart failure (2.3%), was present. Patient characteristics are shown in table 2.

Treatments

In total, 3171 treatments were provided to the participating patients. Based on treatment modality, treatments were divided into 4 groups: MP, MOB, MP+MOB, and "other". Every treatment session with its AE were analyzed separately. Patients' characteristics corresponding with the information on treatment modalities and AE were taken into the analysis. Distribution of characteristics within the 4 treatment modality groups is shown in table 3.

Table 1 Manual therapist characteristics (n=263)

Characteristic	
Age (y), mean ± SD	42.2 (8.4)
Male, n (%)	207 (79%)
Work experience (y), mean ± SD	19.3 (7.1)
Weekly h of work, mean ± SD	24.6 (10.2)
Weekly number of patients with neck pain, mean ± SD	12.2 (8.0)

Table 2 Patient characteristics

Variables	Study Population	Sample	Non-enrolled
Patient characteristics (n= sample)	n=1193	n=686	n=2618
Biological sex (n=681), female (%)	823 (69.4%)	473 (69.4%)	1636 (63.2%) (n=2587)
Age, y (n=669), mean ± SD	44.7 (13.7)	46.4 (13.6)	44.9 (16.6) (n=1856)
Duration of NP, wk (n=613) (%)			
0-6	420 (39.2%)	259 (42.3%)	
6-12	138 (12.9%)	80 (13.1%)	
>12	513 (47.9%)	274 (44.7%)	
Recurrent neck pain (n=644), y (%)	755 (66.9%)	447 (69.3%)	
Marital status (n=659): Married (%)	889 (77.2%)	473 (77.1%)	
Work status (n=666); Employed (%)	897 (77.1%)	491 (73.7%)	
Smoking (n=682), y (%)	300 (25.2%)	161 (23.6%)	
Practicing sports (n=682), y (%)	783 (65.9%)	451 (66.1%)	
Concomitant symptoms (n=684) *	Total: 2190	/ 1832	
Headache n (y, %)	681 (57.0%)	402 (58.8%)	
Low back pain n (y, %)	448 (37.5%)	313 (45.8%)	
Irradiating arm pain n (y, %)	460 (38.5%)	307 (44.9%)	
Disturbed sleep n (y, %)	293 (24.5%)	198 (28.9%)	
Concentration problems n (y, %)	195 (16.3%)	129 (18.9%)	
Memory problems n (y, %)	113 (9.5%)	81 (11.8%)	
NRS now (n=1183), mean (SD, range)	4.8 (2.1, 1-10)	4.9 (2.1, 1-10)	
NDI (n=1096) mean (SD, range)	13.0 (6.5, 0-42)	12.7 (6.4, 0-39)	
NBQ Anxiety and depression (n=1184) mean (SD, range)	3.7 (2.6, 0-10)	4.1 (2.3, 0-11)	

Note. Number in brackets in the 'variables' column are the number of people we have data available for in the sample.
* The total of this item is ≥100% because patients could indicate more than 1 area of concomitant symptoms.

Table 3 Characteristics of patients receiving different treatment modalities

	Manipulation (MP)	Mobilization (MOB)	MP+MOB	No MP nor MOB
Age, y	45.6 (13.2)	47.9 (13.6)	48.2 (13.4)	46.1 (13.6)
Biological sex, female	69.7%	68.3%	64.6%	70.6%
Smoking, yes	23.4%	25.5%	22.2%	26.9%
Comorbidity				
• Hypertension	4.0%	4.2%	4.5%	3.6%
• (History of) heart failure	2.3%	2.8%	2.8%	2.3%
• Hypercholesterolemia	0.8%	0.8%	0.3%	1.1%
• Migraine	1.7%	1.1%	1.4%	1.8%
• Diabetes	1.0%	1.1%	0.7%	1.4%
• Multiple comorbidity	1.5%	2.2%	2.4%	2.1%
• Absence of comorbidity	88.7%	87.7%	87.8%	87.7%
NRS	4.8 (2.1)	5.0 (2.1)	4.8 (2.1)	4.9 (2.1)
Range	1-10	1-9	1-10	1-10
NDI	12.5 (6.2)	13.1 (6.4)	12.6 (6.2)	13.0 (6.3)
Range	0-39	0-31	0-39	0-36
FABQ	10.3 (6.2)	10.7 (6.4)	10.6 (6.3)	10.7 (6.1)
Range	0-28	0-24	0-24	0-24
NBQ	4.2 (2.3)	4.2 (2.3)	4.0 (2.3)	4.2 (2.3)
Range	0-9.5	0-9.5	0-9.5	0-9.5

Frequencies of non-serious adverse events

No serious AEs were reported within our study.

Within the MP group (in total 1014 sessions), stiffness was the most commonly reported AE (after 58.7% sessions), followed by headache (52.0%), radiation (50.3%), aggravation of complaints (48.2%), and fatigue (45.2%). Reports of vomiting (0.3%), disorientation/confusion (5.3%), and cramps (6.8%) were uncommon after manipulation.

Within the MOB group (in total 829 sessions), stiffness was the most commonly reported AE (after 64.7% sessions), followed by radiation (64.0%), aggravation of complaints (57.0%), fatigue (55.6%), and headache (54.6%). Reports of vomiting (2.2%), disorientation/confusion (7.5%), and blurred vision (12.4%) were uncommon after mobilization.

Within the MP+MOB group (in total 437 sessions), stiffness was the most commonly reported AE (after 62.0% sessions), followed by radiation (56.1%), headache (49.0%), aggravation of

complaints (48.3%), and fatigue (44.6%). Reports of vomiting (0.7%), disorientation/confusion (6.4%), and blurred vision (8.9%) were uncommon after MP+MOB.

Within the other modalities group (in total 891 sessions), stiffness was the most commonly reported AE (after 57.1% session), followed by radiation (55.8%), headache (54.0%), aggravation of complaints (50.4%), and fatigue (49.4%). Reports of vomiting (0.6%), disorientation/confusion (7.4%) and blurred vision (9.4%) were uncommon after treatment with other modalities.

Frequencies of AE within the 4 treatment groups are presented in table 4.

Differences in the occurrence of AE between groups were calculated for all treatments using chi square test. A statistical significant difference (χ^2 (3, n=38,046)=46.7248, P<.001) in occurrence was found, detrimental to mobilizations (table 5).

Risk factors of non-serious adverse events

Binary logistic regression was performed to assess the effect of factors on the likelihood that patients would report an AE. Odds ratios (ORs) greater than 2.0 or smaller than 0.5 were considered to be clinically relevant. ORs are shown in table 6.

Analysis revealed that after MP treatment (1014 sessions in total) several common AEs were to be predicted: headache, stiffness, aggravation, radiation, and fatigue. Headache is predicted by age, pain intensity, smoking, and mean disability. Smoking showed to be the strongest predictor of headache after manipulation (OR 3.33 [95% CI 1.83-5.94]). Stiffness was predicted by smoking and pain intensity. Strongest predictor was smoking (OR 3.10 [95% CI 1.83-5.27]). Radiation was predicted by biological sex, smoking, and mean disability. Smoking also proved to be the strongest predictor of radiation after manipulation, recording an OR of 2.79 [95% CI 1.91-4.08]). The strongest predictor of fatigue after manipulation is again smoking (OR 2.10 [95% CI 1.37-3.22]).

Analysis revealed that uncommon AEs after manual therapy treatment are to be predicted too. The strongest predictor of cramps after manipulation is smoking (OR 2.1 [95% CI 1.37-3.22]). With regard to nausea after manipulation, biological sex was associated, reporting an OR of 0.49 (95% CI 0.28-0.86) indicating that men had 51% lower odds of experiencing nausea after treatment with manipulation than women. The presence of comorbidity was the strongest predictor of nausea after manipulation, reporting an OR of 3.33 (95% CI 1.30-8.55).

A total of 829 treatments consisted of MOB. Analysis showed that after MOB, stiffness, aggravation of complaints, radiation and nausea were to be predicted from the factors included in the analysis. Stiffness was predicted by pain intensity and presence of comorbidity, recording an OR of 3.65 (95% CI 1.26-10.58). Biological sex was associated, reporting an OR of 0.22 (95% CI 0.11-0.46), indicating that men had 78% lower odds of experiencing stiffness after MOB than woman. For aggravation of complaints, the presence of comorbidity is a strong predictor, recording an OR of 3.88 (95% CI 1.62-9.26). Radiation is also predicted by the presence of comorbidity (OR 2.32 [95% CI 1.22-4.44]) as well as nausea after MB treatment (OR 2.59 [95% CI 1.07-6.29]). Smoking is inversely associated with vertigo after mobilization, recording an OR of 0.38 (95% CI 0.15-0.99).

After treatment with MP+MOB within 1 session, radiation was reported as an AE and analysis revealed that it can be predicted by smoking (OR 2.84 [95% CI 1.58-5.12]). Analysis revealed that the occurrence of fatigue is predicted by smoking as well (OR 2.70 [95% CI 1.70-4.30]). Men have lower odds of reporting fatigue

Table 4 Descriptives of the occurrence of non-serious AE within treatment groups

	Manipulation (MP) (1014 sessions)		Mobilization (MOB) (829 sessions)		MP+MOB (437 sessions)		"Other modalities" (891 sessions)	
	% of treatments after which AE occurs	Mean intensity (1-10) (SD) range reported	% of treatments after which AE occurs	Mean intensity (1-10) (SD) range reported	% of treatments after which AE occurs	Mean intensity (1-10) (SD) range reported	% of treatments after which AE occurs	Mean intensity (1-10) (SD) range reported
Headache	52.0%	4.6 (2.0) 2-10	54.6%	4.6 (2.0) 2-10	49.0%	4.4 (1.9) 2-10	54.0%	4.6 (1.9) 2-9
Radiation	50.3%	4.3 (1.6) 2-10	64%	4.8 (1.8) 2-9	56.1%	4.6 (1.8) 2-10	55.8%	4.6 (1.9) 2-10
Aggravation of complaints	48.2%	4.6 (1.9) 2-10	57%	4.9 (1.9) 2-9	48.3%	4.8 (1.9) 2-10	50.4%	4.6 (1.8) 2-10
Fatigue	45.2%	4.5 (1.8) 2-9	55.6%	4.7 (2.0) 2-9	44.6%	4.8 (1.9)	49.4%	4.8 (1.9) 2-9
Stiffness	58.7%	4.3 (1.6) 2-10	64.7%	4.4 (1.8) 2-9	62.0%	4.4 (1.8) 2-10	57.1%	4.3 (1.8) 2-10
Cramps	6.8%	4.3 (2.0) 2-9	13.7%	4.1 (1.7) 2-8	8.9%	4.1 (1.4) 2-7	12.0%	3.9 (1.7) 2-9
Dizziness	24.5%	3.9 (1.8) 2-8	38.9%	4.0 (1.8) 2-9	24.0%	4.1 (1.9) 2-9	26.2%	4.2 (1.8) 2-9
Blurred vision	8.7%	3.7 (1.5) 2-8	12.4%	3.8 (1.6) 2-7	8.9%	3.6 (1.6) 2-8	9.4%	4.3 (2.0) 2-8
Nausea	11.1%	4.3 (1.7) 2-8	23.2%	3.7 (1.5) 2-8	12.4%	4.1 (1.5) 2-8	12.3%	4.4 (1.7) 2-8
Tinnitus	7.3%	1.2 (0.7) 1-6	19.9%	3.6 (1.6) 2-7	11.0%	3.4 (1.3) 2-6	10.6%	3.5 (1.6) 2-7
Vomiting	0.3%	5.0 (1.7) 4-7	2.2%	3.6 (1.9) 2-7	0.7%	5.0 (1.7) 3-6	0.6%	4.0 (1.3) 3-6
Limb weakness	19.6%	4.1 (1.7) 2-9	25.8%	4.5 (2.1) 2-10	22.7%	4.1 (1.8) 2-8	21.4%	4.2 (2.0) 2-10
Disorientation/Confusion	5.3%	3.5 (1.4) 2-9	7.5%	3.7 (1.9) 2-9	6.4%	3.4 (1.7) 2-9	7.4%	4.9 (2.2) 2-9

NOTE. AE is defined as intensity >1. Dark gray indicating the highest prevalence rates, light gray indicating second highest prevalence rates.

Table 5 Chi square test between treatment groups

		MP	MOB	MP+MOB	No MP nor MOB 'Other'	**Total**
X^2 *(3, n= 38,046)= 46.7248*	Present n (%)	1162 (10%)	1224 (12.3%)	547 (10.4%)	1217 (11.4%)	**4150**
	Absent n (%)	11,003 (90%)	8723 (87.7%)	4697 (89.6%)	9473 (88.6%)	**33,896**
P<.001	**Total***	**12,165 (100%)**	**9947 (100%)**	**5244 (100%)**	**10,690 (100%)**	**38,046**

NOTE. Differences (%) in the occurrence of AE between treatment groups for all treatments.
* Total within all 13 AE.

and stiffness after MP+MOB, with ORs of 0.39 (95% CI 0.21-0.73) and 0.28 (95% CI 0.095-0.85). The occurrence of tinnitus as an AE after treatment was predicted by female sex (OR 3.51 [95% CI 1.83-6.71]). The OR >1 indicates that men are more likely to report tinnitus after MP+MOB. Smoking is inversely associated with vertigo after MP+MOB, recording an OR of 0.38 (95% CI 0.15-0.99). With regard to nausea after MP+MOB, biological sex was associated, reporting an OR of 0.30 (95% CI 0.14-0.87), which indicates that men have lower odds of experiencing nausea after treatment with MP+MOB than women.

Although AEs are common after treatment with MP or MOB, they frequently occur after treatment with "other modalities" as well. The occurrence of headache, stiffness, fatigue, and nausea were predicted by factors included in the analysis. For headache after treatment with other modalities, smoking is the strongest risk factor (OR 2.39 [95% CI 1.35-4.24]). The same goes for stiffness after treatment with other modalities (OR 2.19 [95% CI 1.30-3.66]). Men have lower odds of reporting stiffness than women (OR 0.26 (95% CI 0.10-0.66). Radiation and fatigue are also predicted by smoking ([OR 2.86 (95% CI 1.96-4.1]) and (OR 2.70 [95% CI 1.7-4.3])). Presence of comorbidity predicts nausea after treatment with "other modalities" (OR 2.99 [95% CI 1.16-7.73]). Presence of comorbidity is inversely associated with vertigo and weakness of the limbs after "other modalities", recording ORs of 0.45 (95% CI 0.22-0.91) and 0.47 (95% CI 0.29-0.76). Smoking is inversely associated with the effects of vertigo after "other modalities", recording an OR of 0.37 (95% CI 0.18-0.77).

Discussion

The aim of the current study was to gain insight into the occurrence of serious and non-serious AE after spinal manipulation and mobilization in patients with neck pain. Secondly, we wanted to explore the risk factors of AE after spinal manipulation and mobilization in patients with neck pain. Fortunately, no serious AEs were reported. One remarkable finding was that there seems to be a statistical difference in the occurrence of non-serious AE after HVT manipulation and non-thrust mobilization, detrimental to mobilizations. When the occurrence of AE after manipulations is compared with the occurrence of AE after a treatment with "other modalities" (eg, information and advice, massage, transcutaneous electro neuro stimulation, coaching, questionnaires), no differences in occurrence appear to be present.

Another remarkable finding in our study was that smoking (OR ranges from 2.10 [95% CI 1.37-3.22] to 3.33 [95% CI 1.83-5.93]) and the presence of comorbidity (OR ranges from 2.32 [95% CI 1.22-4.44] to 3.88 [95% CI 1.62-9.26]) had the strongest associations with reporting AEs after manual therapy treatment.

Although cervical spine manipulation was considered primarily to be related to AE, there seems to be a significant difference in the occurrence of non-serious AEs detrimental to non-thrust mobilizations in our cohort.

The cervical spine was defined as the region between C0 and C6, whereas treatment on C7-T1 and treatment in the thoracic spine were excluded from analysis. Although manipulation of the thoracic spine is a commonly chosen treatment technique in patients with neck pain,[28] we excluded it from the analysis, since we were interested in the occurrence of AE after manual therapy treatment in the cervical spine.

The number of AEs reported in our study is higher than in other studies.[6,24] In other studies, when more than 1 AE was reported, only the most severe or the longest lasting AE is chosen to be included in the analysis. In our study, we analyzed all reported AEs, which may have led to a higher prevalence rate. Comparison with other studies is difficult, because of differences in reporting.

According to Cagnie et al,[6] we have chosen to classify a treatment session as an MP session when spinal manipulation was used, regardless of the number of manipulations within the session. Cagnie et al[6] found that the number of performed manipulations could not be associated with the occurrence of AE. The direction and precise location in which the manipulation has been applied might be of interest. Further analysis should reveal whether 1 or more directions or locations of the manipulation could increase the chance of experiencing an AE after treatment.

Occurrence of adverse events

No serious AEs were reported in this cohort study. It is, however, possible that some non-serious AE have persisted or aggravated after 48 h. No data are available about the continuation of these events after 48 h.

Manipulation

When both groups were compared, the MP group and the other treatment groups had similar prevalence rates of AE.

Mobilization

Previous studies have suggested that when comparing spinal manipulation with spinal mobilization, the treatment effect seems to be the same, but the presence of AE appears to be more common among patients treated with manipulation.[21,29,30] Little is published in literature about the occurrence of AE after mobilization. In our study, we found AE to occur more frequent after mobilization than after manipulation treatment. Because little is known about the etiology of AE, it is hard to explain the differences in occurrence of AE between manipulation and mobilization. Manipulation techniques have been under debate for their possible serious AEs. These serious AEs are rare, whereas the non-serious AEs are far more frequently reported. Vautravers and Maigne[31] claim that cervical spine manipulations should be contra-indicated for patients who experience dizziness, nausea, or headache persisting for more than 2 days. Ignoring these AEs increases the likelihood of harming the patient. Based on the outcome of our study, the question is raised whether this applies to mobilization too.

Table 6 Outcome of logistic regression analysis

Factors Entering the Model		Manipulation (MP) (1014 sessions)	Mobilization (MOB) (829 sessions)	MP+MOB (437 sessions)	No MP nor MOB (891 sessions)
Common		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Headache	Age, y*	.97 (.95-.99)	.98 (.96-.99)	.95 (.91-.98)	.97 (.95-.99)
	Pain intensity*	1.32 (1.09-1.61)			1.31 (1.09-1.58)
	Smoking (yes) †	***3.33 (1.83-5.94)***			***2.39 (1.35-4.24)***
	Disability*	1.09 (1.04-1.13)	1.12 (1.06-1.19)		1.07 (1.03-1.11)
	Anxiety + depression*				1.24 (1.06-1.45)
Radiation	Biological sex†	.65 (.42-.99)			1.57 (1.03-2.38)
	Age, y*		1.01 (1.0-1.03)		
	Smoking (yes) †	***2.79 (1.91-4.08)***	1.57 (1.05-2.36)	***2.84 (1.58-5.12)***	*2.86 (1.96-4.18)*
	Pain intensity*		1.26 (1.12-1.42)	1.22 (1.02-1.45)	1.16 (1.04-1.30)
	Presence of comorbidity†		***2.32 (1.22-4.44)***		
	Anxiety + depression*				1.11 (1.003-1.23)
	Fear Avoidance*			1.08 (1.03-1.34)	
	Disability*	.96 (.94-.98)			
Aggravation complaints	Smoking (yes) †	1.7 (1.11-2.58)			
	Disability*		1.03 (1.01-1.05)		1.02 (1.001-1.05)
	Presence of comorbidity†		***3.88 (1.62-9.26)***		
	Fear avoidance*	.96 (.93-.99)			
	Anxiety + depression*	1.20 (1.08-1.34)	1.16 (1.04-1.29)		1.31 (1.18-1.46)
Stiffness	Age, y*				.97 (.95-.98)
	Biological sex †		***.22 (.11-.46)***	***.28 (.095-.85)***	***.26 (.10-.66)***
	Smoking (yes) †	***3.10 (1.83-5.27)***			***2.19 (1.3-3.66)***
	Pain intensity*	1.26 (1.08-1.48)	1.22 (1.05-1.43)		1.18 (1.01-1.38)
	Presence of comorbidity†		***3.65 (1.26-10.58)***		
Fatigue	Biological sex†	.58 (.35-.95)	.52 (.31-.89)		
	Age, y*		.98 (.97-.99)		
	Smoking (yes) †	***2.10 (1.37-3.22)***		***2.70 (1.7-4.30)***	***2.70 (1.7-4.3)***
	Pain intensity*	1.16 (1.04-1.30)			
	Disability*	.95 (.93-.97)	.97 (.95-.99)		.96 (.94-.98)
	Presence of comorbidity†			***.39 (.21-.73)***	***.40 (.21-.73)***
	Anxiety +depression*	1.16 (1.04-1.30)	1.14 (1.01-1.30)	1.28 (1.12-1.46)	1.28 (1.12-1.46)
Uncommon					
Cramps	Biological sex †	.58 (.35-.95)			
	Age, y*			1.03 (1.01-1.06)	
	Smoking (yes) †	***2.10 (1.37-3.22)***	1.79 (1.12-2.87)		
	Pain intensity*	1.16 (1.04-1.30)	1.25 (1.08-1.44)		
	Disability	.95 (.93-.97)			
	Fear avoidance*		.97 (.93-1.17)		1.06 (1.02-1.1)
	Anxiety + depression*	1.16 (1.04-1.30)			
Dizziness	Biological sex†		.57 (.40-.81)		
	Age, y*				.98 (.97-.99)
	Disability*	1.04 (1.02-1.06)			1.02 (1.001-1.04)
	Anxiety+ depression*	1.16 (1.06-1.26)	1.13 (1.04-1.24)	1.16 (1.01-1.32)	1.19 (1.09-1.3)
	Presence of comorbidity†				.55 (.35-.88)
Blurred vision	Pain intensity*			1.31 (1.04-1.65)	1.25 (1.08-1.44)
	Disability*				1.04 (1.01-1.07)
Nausea	Age, y*		.98 (.97-.998)		
	Anxiety + depression*				1.26 (1.12-1.43)
	Biological sex†	***.49 (.28-.86)***	.59 (.36-.96)	***.30 (.14-.67)***	***.49 (.27-.87)***
	Pain intensity*		1.28 (1.12-1.46)		
	Disability*	1.1 (1.02-1.08)	1.04 (1.01-1.07)		
	Fear Avoidance		.95 (.91-.98)		.97 (.93-.99)
	Presence of comorbidity†	***3.33 (1.30-8.55)***	***2.59 (1.07-6.29)***		***2.99 (1.16-7.73)***
Tinnitus	Disability*	1.06 (1.02-1.10)			1.05 (1.02-1.09)
	Biological sex †		1.80 (1.21-2.69)	***3.51 (1.83-6.71)***	
	Age, y*			1.03 (1.001-1.05)	1.03 (1.01-1.05)

(*continued on next page*)

Table 6 (*Continued*)

Factors Entering the Model		Manipulation (MP) (1014 sessions)	Mobilization (MOB) (829 sessions)	MP+MOB (437 sessions)	No MP nor MOB (891 sessions)
Vomiting	Age, y*	.90 (.81-.96)			
	Disability*		1.23 (1.07-1.40)	1.52 (1.05-2.21)	1.56 (1.12-2.18)
Vertigo	Age, y*	.97 (.96-.99)			.98 (.96-.99)
	Smoking (yes) †	***.25 (.09-.71)***	***.38 (.15-.99)***	***.38 (.15-.99)***	***.37 (.18-.77)***
	Pain intensity*				.79 (.67-.93)
	Disability*	.96 (.93-.99)			1.04 (1.01-1.08)
	Presence of comorbidity†				***.45 (.22-.91)***
	Anxiety + depression*	1.25 (1.06-1.47)	1.27 (1.06-1.51)	1.27 (1.06-1.51)	1.42 (1.21-1.67)
Weakness of the limbs	Biological sex†			.57 (.33-.97)	
	Presence of comorbidity†				.47 (.29-.76)†
	Pain intensity*		1.18 (1.06-1.32)	1.26 (1.08-1.48)	
	Anxiety + depression*		1.18 (1.08-1.31)		1.22 (1.11-1.34)

NOTE. Empty cells did not significantly contribute to the model NB. Only variables which significantly contribute to the model are presented, italicized values are defined as clinically relevant (OR >2 or OR <0.5).

* Continuous variables.

† Dichotomous variables.

Manipulation and mobilization

It could be hypothesized that when a patient receives MP as well as MOB within 1 treatment session, reported AE rates should be higher than with a single modality. Our study shows that this is not what happens in clinical practice. Reported non-serious AEs are high, but not higher than in the MOB group (table 5). A possible explanation for this phenomenon is that when 2 treatment modalities are applied within 1 treatment session, the number of applied techniques decreases. On the other hand, the number of applied techniques seems of no consequence.[6]

Other modalities

We have chosen to create 1 group of treatment consisting of other modalities than MP or MOB. This group serves as a "control group" and is representative based on the fact that it contains patient characteristics that are similar to the other treatment groups. The fact that the prevalence rates of AE in this group is as high as in the MP, MOB, and MP+MOB group (table 5) suggests that AE are common, no matter what modality is applied.

Limitations of the study

The results of our study should be viewed within the limitations of the study. From the 1193 patients enrolled in the study, only 686 (57.5%) returned a complete set of data before deadline. We choose to ask the patients to return their questionnaires and report AE to the research center without the interference of the MT, in order to avoid socially desirable answers and responder bias. This, however, caused loss of data.

Given that it is a longitudinal cohort study of the occurrence of AE within usual care manual therapy, patients are not randomized. Patients' characteristics may a priori have contributed to the clinical decision of the manual therapist to apply manipulation or mobilization or other modalities.

There are different ways to classify AE. In another study, a classification based on the occurrence of neurologic symptoms vs non-neurologic symptoms was used.[32] Little is known about the etiology of AE[33] and therefore we choose not to classify based on whatever *seems to be* a neurologic AE, but choose only to classify based on the intensity and duration of the patients' reported AEs.[34,35] The differences in presenting the outcome highlight the complexity of accurately reporting AE.[36]

We have chosen to analyze from the perspective of the treatment modality and to include patient characteristics and other factors as covariates into the regression analysis. Because every treatment episode has been split up into separate treatments, patient characteristics may/can be present in MP group, as well as in MOB group, MP+MOB group, and the "other treatments"-group, which might lead to over-representation. We suggest the recommendation that future research should include a propensity-score analysis, so that possible confounding based on the overlap of patient characteristics is compensated for.

In our study, we asked patients to report AEs within 48 h after treatment, to avoid having too big a time interval which could affect the accuracy of reporting. We unfortunately have no information on how long the AE lasted after 48 h.

We did not include oral contraceptives in our study. Oral contraceptives are described as a risk factor for AE after spinal manipulative treatment. In the study of Cagnie et al,[6] the use of oral contraceptives did not show any difference in the type of AE.

It is difficult to determine whether the AE that arose were caused by the treatment provided. AE could be caused by other activities, or factors not covered in the questionnaire such as pre-existing problems, lifestyle, environmental effects, or concurrent treatment by other health care professionals.[6,20]

The focus of this study was to explore the role of patient characteristics in the occurrence of (N)SAE after manual therapy treatment. More research is needed to investigate the dose-response relation between the different treatment modalities and the occurrence of (N)SAE.

Conclusion

Our analysis showed a statistically significant difference in the occurrence of non-serious AEs between treatments consisting of manipulation, mobilization, a combination of both or even "other modalities" detrimental to mobilizations. In our study, no serious AEs were reported, which underlines the rare occurrence of these serious AEs. Non-serious AEs in manual therapy practice are

common and can be predicted by smoking (OR ranges from 2.10 [95% CI 1.37-3.22] to 3.33 [95% CI 1.83-5.93]) and the presence of comorbidity (OR ranges from 2.32 [95% CI 1.22-4.44] to 3.88 [95% CI 1.62-9.26]).

Keywords

Adverse event; Cohort study; Manual therapy; Manipulation; Neck pain; Rehabilitation; Risk factors

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