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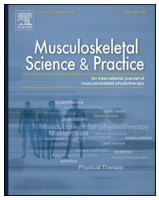

Original article

Non-serious adverse events do not influence recovery in patients with neck pain treated with manual therapy; an observational study

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1. Introduction

Up to 70% of individuals experience an episode of neck pain (NP) once in their life (Fejer et al., 2006). The course of NP is often episodic; evidence indicates that between 50 and 75% of people who experience NP at some initial point will still report NP 1–5 years later (Carroll et al., 2009). In a Dutch study, 47% of the patients in primary care reported to have ongoing NP (Vos et al., 2008). A recurrent course is common with almost 25% of patients reporting aggravation of NP after full recovery (Chaibi et al., 2021; C ô t é et al., 2004). Consequently, the estimated economic burden of NP is substantial (Hoy et al., 2014).

Physiotherapy, with or without manual therapy (MT) techniques, and chiropractic are common treatment options for patients with NP (Chaibi et al., 2021). Physiotherapy for NP is diverse and commonly used MT techniques include spinal manipulations, spinal mobilisations, exercise, and information and advice (Gross et al., 2015). Despite evidence to support the benefits of cervical manipulation and mobilisation (Gross et al., 2015), the use of these treatment modalities remains a matter of debate because of their potential risks of serious adverse events (SAEs), e.g. stroke, cervical artery dissection, transient ischemic attack. (Cagnie et al., 2004)' (Ernst, 2007)' (Rubinstein et al., 2007) However, the occurrence of SAEs seems rare (Kerry and Taylor, 2014; Chaibi and Russell, 2019). Besides these SAEs, several non-serious adverse events (NSAEs) e.g. aggravation of complaints, stiffness, irradiating pain are described. Other than SAEs, the NSAEs after MT are common, benign, and transient (Cagnie et al., 2004; Rubinstein et al., 2008). The incidence of minor or moderate transient adverse events after MT was estimated as 41% from cohort studies and 22% from randomised controlled trials (Carnes et al., 2010). Another study showed that half of patients experience minor to moderate adverse events after MT treatment, with most NSAEs being musculoskeletal or pain-related (Rubinstein et al., 2008). It is generally assumed that there is an under-reporting of cases with (N)SAEs (Carnes et al., 2010; Kranenburg et al., 2017).

Patient characteristics such as age, gender, fear avoidance, concomitant symptoms, previous musculoskeletal complaints, patient expectancies, poor general health, and smoking, as well as pain-related factors such as pain intensity, duration of pain, and recurrence of NP are

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known to influence recovery (Groeneweg et al., 2017; Artus et al., 2017; Bier, 2016; Walton et al., 2013; Carroll et al., 2008; Palml ö f et al., 2016). However, it is unknown whether NSAEs can influence recovery after multimodal treatment including MT in patients with NP. Therefore, our research question was: What is the influence of NSAEs, additional to other prognostic factors, on perceived recovery in patients with NP treated with usual multimodal care inclusive of MT?

2. Methods

2.1. Design

A prospective multicentre cohort study with 12-month follow-up was conducted in primary care physiotherapy in the Netherlands of which the current study used the post-treatment follow-up data. The Medical Ethical Committee of the Erasmus MC Rotterdam approved this study. The design of the complete study was published elsewhere (Peters et al., 2019). The reporting of this study was guided by the STROBE statement (Von Elm et al., 2007).

2.2. Physiotherapists with postgraduate qualifications in MT

During a 3-month inclusion period, patients with NP were recruited by 263 participating physiotherapists with postgraduate qualifications in MT in The Netherlands. The physiotherapists provided usual care to their patients with NP. Although the definition of usual care has not been standardised, it includes the routine care received by patients for prevention or treatment of diseases (Harlapur et al., 2013). The type of routine care can vary by the grade of neck pain and severity, the practice in which patients present themselves, and individual therapists. Physiotherapy in our study is mostly provided in the context of a multimodal management program including information, advice, MT and exercise.

2.3. Patients

Patients with non-specific NP of any duration and aged between 18 and 80 years of age were eligible for inclusion in the study. Exclusion criteria were not being able to fluently read and write the Dutch language and having specific NP due to severe trauma, systemic disorders, or generalised neurologic syndromes. Patients reported on (N)SAEs within 48 h after every treatment session. All patients signed an informed consent prior to enrolment in the study.

2.4. Outcome measures

A literature search in the databases MEDLINE (PubMed), CINAHL, Embase, and PEDro was conducted to identify potentially relevant prognostic factors on outcomes of MT. Age (Walton et al., 2013; Feleus et al., 2007; Bruls et al., 2013; Bot et al., 2005; Keijsers et al., 2010), gender (Vos et al., 2008), pain intensity (Walton et al., 2013; Bot et al., 2005; Hoving et al., 2004), recurrent NP (Carroll et al., 2009), disability (Artus et al., 2017), duration of pain (Artus et al., 2017; Mallen et al., 2007), fear avoidance (Mallen et al., 2007), concomitant symptoms (Vos et al., 2008; Walton et al., 2013; Feleus et al., 2007; Bot et al., 2005; Keijsers et al., 2010; Leaver et al., 2013), patient expectancies (Bischop et al., 2013), smoking (Vineis, 2008), and sport participation (Hoving et al., 2004) were identified and measured at baseline. NP characteristics included intensity as measured by the Numeric Rating Scale (NRS, range 1–10) and patients' self-reported recurrence and duration (<6 weeks; acute, >6 but <12 weeks; subacute, or >12 weeks; chronic NP). The Neck Disability Index (NDI) was used to measure disability due to NP (range 0–50) (Schellingerhout et al., 2012; Vernon, 2008). The Fear Avoidance Beliefs Questionnaire (FABQ subscale physical activities (FABQ-PA) range 0–30) (Landers et al., 2008; Cleland et al., 2008) was used to measure avoidance of physical activities due to fear of NP. Additionally, patients were asked to provide additional information on possible risk factors for (N)SAEs such as comorbidities (e.g., hypertension, (history of) heart failure, diabetes mellitus, hypercholesterolemia, atherosclerosis, migraine). (Paanalahti et al., 2014)' (Haldeman et al., 1999)' (Haldeman et al., 2002)

During the treatment period, patients reported on (N)SAEs using the Adverse Events Questionnaire (AEQ), which was filled out by the patient within 48 h after each treatment. The AEQ has been used before (Cagnie et al., 2004; Rubinstein et al., 2007; Hurwitz et al., 2005) and consists of several questions on possible reactions potentially occurring after treatment. The AEQ measures if the patient experienced any unpleasant reaction after treatment, and, additionally, the type of reaction, time of onset (range 1–4), duration (range 1–4), and intensity of symptoms (range 1–10) (See Appendix 1). In order to grade NSAEs, we decided that the occurrence of *uncommon* NSAEs such as cramps, dizziness, blurred vision, nausea, tinnitus, vomiting, dizziness, and weakness of the limbs are undesirable and their occurrence (intensity >1 on the 10-point NRS) was defined as NSAEs. For *common* NSAEs like headache, stiffness, aggravation of complaints, radiating pain, and fatigue, the intensity should be > 5 on the 10-point NRS and the duration longer than 24 h to be defined as a NSAE. All other reactions of lesser intensity and duration were defined as 'absence of an (N)SAE'. (N)SAEs were registered throughout the treatment episode and dichotomised as 'present' or 'absent', regardless the number of adverse events, the number of treatment sessions, or the treatment modality applied.

At the end of the treatment episode, the primary outcome, patients' self-rated recovery, was assessed using the Global Perceived Effect (GPE) scale. The GPE is scored on a 7-point Likert scale ranging from 'total recovery' to 'worse than ever'. *A priori*, recovery was defined as 'total recovery', 'much improved' or 'somewhat better' as reported by the patient. Being a single question, GPE is easy and quick to administer and the results are seemingly simple to interpret. Test-retest reliability of the GPE is excellent (Kamper et al., 2010). After collecting the data, treatments were categorised into manipulation, mobilisation, manipulation and mobilisation or 'other treatment modalities', including information/advice and exercise. The distribution of applied modalities and their reported (N)SAEs are shown in Appendix 2.

2.5. Data analysis

Differences in gender were tested using the chi-square test, and differences in age between patients who filled out and those who did not fill out the GPE did not have normal distribution and were therefore tested using Mann-Whitney U tests. Univariable and multivariable logistic regression analyses were performed to estimate the relationship between potential prognostic factors and perceived recovery, measured by the GPE. The independent variables in these models were selected from NSAEs, gender, age, initial pain, recurrent NP, duration of NP, concomitant complaints, expectancies with regard to recovery, disability, fear avoidance, smoking, and sport participation. All independent variables with P values < 0.2 in univariable analysis were included in the subsequent multivariable logistic regression analysis. The independent variables were checked for correlation to prevent multicollinearity. In case of high correlation, one of the two variables was selected based on lower correlation with other independent variables. Univariable associations between independent variables and the outcome were expressed as odds ratios (OR) with their 95% confidence intervals (CI).

Subsequently, multivariable logistic regression analysis was applied to test prognostic variables for perceived recovery measured by GPE immediately after the multimodal treatment episode. To account for missing values in the data, multiple imputation using fully conditional specification was applied (25 iterations). Based on the evidence (Carroll et al., 2009; Artus et al., 2017; Walton et al., 2013) gender, age, and initial pain were forced as independent variables into the analysis. To estimate the added prognostic value of AE on GPE (additional to the other independent variables), two separate logistic regression models

were constructed; one model without NSAEs and one with NSAEs included. The explained variance was calculated using Nagelkerke's R^2. The Hosmer-Lemeshow test was performed to assess how well the model fits the data (Hosmer and Lemeshow, 2010). Associations between independent variables and the outcome were expressed as odds ratios (OR) with their 95% confidence intervals (CI). The dichotomous dependent variable 'GPE' was coded as '1' (no recovery) and '0' (recovery). To prevent overfitting, the total number of variables included in this model was limited to eight variables according to the one-in-ten-rule (Steyerberg et al., 2000). The significance level was set at $\alpha = 0.05$. Data were analysed using the IBM SPSS 24 software package.

3. Results

3.1. Study flow and baseline measurements

Two hundred and sixty-three physiotherapists with postgraduate qualifications in MT participated in the study and enrolled patients during the recruitment period. The majority of the physiotherapists were male (79%), aged ≥40 years, with a mean of 20 years of clinical working experience.

During the recruitment period, 1311 patients were eligible and 1193 patients with NP provided baseline measurements (Fig. 1). Mean age (SD) of the participating patients was 44.7 (13.7) years and 823 (69.4%) participants were female. Five hundred and thirteen (47.9%) patients had NP longer than 12 weeks and 755 (66.9%) had recurrent NP. Five hundred and eighty-one (48.6%) participants filled out the GPE post-treatment and 460 (79%) of patients reported to be recovered. Table 1 presents the baseline characteristics of the study sample. There was a significant difference in age between patients who filled out a GPE questionnaire (median age 47 years), and those who did not (42 years) ($p < 0.001$), but there was no significant difference ($X^2(df = 1) = 2.028$, $p = 0.166$) in gender. In our sample, no SAE occurred. A number of 297 (51%) patients reported a NSAE during a treatment episode.

Missing value analysis showed that the percentage of missing values per variable ranged between 0 and 10.4%. Within the cases that filled out the GPE (n = 581), missings were completely at random (Little's MCAR, $X^2(df = 8) = 3.079$, $p = 0.929$.

3.2. Univariable analyses

Univariable associations are shown in Table 2. The duration of NP at baseline (acute NP OR 0.39 (95% CI 0.19–0.81), $p < 0.001$ and subacute NP (OR 0.32 (95% CI 0.19–0.52), $p = 0.012$)), with chronic NP serving as a reference category, recurrent NP (OR 1.43 (95% CI 0.91–2.24), $p = 0.117$), fear avoidance (OR 1.03 (95% CI 1.00–1.03), $p = 0.077$), and patient expectancies (OR 3.78 (95% CI 0.53–27.08) ($p = 0.186$)) were associated with perceived recovery and were subsequently entered into the multivariable analysis.

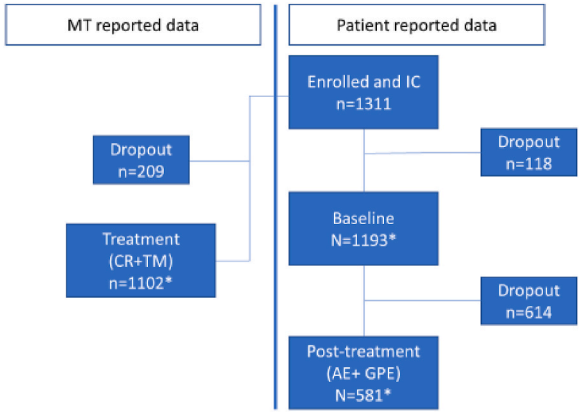

Fig. 1. Flow chart of the study.

Table 1
Patient characteristics and baseline measures.

	Study population	Non-participants
Variables	Baseline (n = 1193)	Baseline (n = 2618)
Age (n = 1170), mean (sd)	44.7 (13.7)	44.9 (16.6) (n = 2587)
Gender (n = 1186), female (%)	823 (69.4%)	1636 (63.2%) (n = 1856)
Duration (n = 1072) (%)		
Acute 0–6 wks	420 (39.2%)	
Sub-acute 6–12 wks	138 (12.9%)	
Chronic >12 wks	513 (47.9%)	
Concomitant symptoms: n = 1096		
Total reported: 2382[a]		
Headache yes (%)	707 (64.5%)	
Low back pain yes (%)	538 (49.1%)	
Irradiating pain yes (%)	536 (48.9%)	
Disturbed sleep yes (%)	293 (26.7%)	
Concentration problems yes (%)	195 (17.8%)	
Memory loss yes (%)	113 (10.3%)	
Recurrent NP (n = 1129) yes (%)	755 (66.9%)	
NRS now (n = 1183), mean (sd, range)	4.8 (2.1; 1–10)	
NDI (n = 1096) mean (sd, range)	13.0 (6.5, 0–42)	
FABQ (n = 1053) mean (sd, range)	26.6 (16.6; 0–85)	
FABQ-W (n = 1103) mean (sd, range)	13.4 (12.2; 0–60)	
FABQ-PA (n = 1129) mean (sd, range)	13.2 (7.3; 0–30)	
PEL Expected recovery due to: 1. total treatment (n = 1190)	1179 (99.1%)	

[a] The total of this item is ≥ 100% because patients could indicate more than one area of concomitant symptoms. FABQ, Fear-Avoidance Beliefs Questionnaire; FABQ-W, Fear-Avoidance Beliefs Questionnaire 'work'-subscale; FABQ-PA, fear-avoidance beliefs questionnaire 'physical activity'-subscale; NDI, Neck Disability Index, ranging from 0 (no disability) to 50 (complete disability); NP, neck pain; NRS, Numeric Rating Scale, ranging from 1 (no pain) to 10 (worst pain); PEL, patient expectancy list, 5-point Likert scale; scores based on 'most likely' and 'likely'.

3.3. Multivariable analyses

Seven independent variables (age, gender, pain intensity, duration of NP, recurrent NP, fear avoidance, patient expectancies) were entered into the multivariable model. The full model containing all variables was statistically significant ($p < 0.001$). The model as a whole explained 9.5% (Nagelkerke R^2) of the variance in recovery and correctly classified 81.5% of patients. The Hosmer-Lemeshow test indicated that the model adequately fitted the data ($p > 0.05$). ORs and CI are presented in Table 2. Duration of NP at baseline made an independent statistically significant contribution to the model, recording an OR of 0.39 (95% CI 0.24–0.64) for acute NP as compared with chronic NP. For subacute NP, an OR of 0.46 (95% CI 0.23–0.95) was found. The values of these odds ratios suggest that the longer a patient suffers from neck pain, the less likely it is that a patient recovers. No other variables were found to be significantly associated with recovery in this model and therefore our next analysis contained age, gender, pain intensity, and duration of NP as independent variables. This model was statistically significant ($p < 0.001$), with an explained variance in the reporting of recovery of 7.3% (Nagelkerke R^2). The Hosmer-Lemeshow test showed goodness of fit ($p > 0.05$). ORs and confidence intervals are presented in Table 2.

Adding NSAE to the independent variables showed that NSAE did not significantly contribute to the model, with $p = 0.351$ and an OR of 1.24 (95% CI 0.79–1.94) (Table 2). Acute NP at baseline made an independent statistically significant contribution to the model with an OR of 0.40 (95% CI 0.26–0.64). For subacute NP an OR of 0.45 (95% CI 0.22–0.90) was found.

Table 2
Logistic regression analysis of variables' association with outcome on GPE.

	Univariable			Multivariable without AE			Multivariable with AE		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	1.01	1.00–1.03	***0.139****	1.01	0.99–1.02	0.286	1.01	0.99–1.03	0.245
Gender	1.03	0.66–1.61	***0.887****	0.93	0.58–1.49	0.759	0.98	0.61–1.56	0.919
Pain intensity	1.01	0.92–1.11	***0.860****	0.99	0.89–1.11	0.934	1.02	0.92–1.13	0.742
Duration of NP			***0.000***						
Chronic (ref)	ref			***ref***			***ref***		
Acute	***0.32***	***0.19-0.52***		***0.39***	***0.24-0.64***	***0.000***	***0.40***	***0.25-0.64***	***0.000***
Subacute	***0.39***	***0.19-0.81***		***0.46***	***0.23-0.95***	***0.035***	***0.45***	***0.22-0.90***	***0.025***
Recurrent NP	1.43	0.91–2.24	***0.117***	1.26	0.79–2.01	0.325			
Disability (NDI sum)	1.01	0.98–1.04	0.575						
Fear-avoidance (FABQ PA sum)	1.03	1.00–1.06	***0.077***	1.03	0.99–1.06	0.075			
Concomitant complaints	1.23	0.71–2.12	0.466						
Smoking	1.31	0.82–2.11	0.259						
Sports	0.84	0.55–1.29	0.428						
Expectations (PEL)	3.78	0.53–27.08	***0.186***	0.68	0.09–5.24	0.713			
AE during treatment	1.26	0.82–1.94	***0.287****				1.24	0.79–1.94	0.351

Variable with association $p < 0.2$ in univariable (italicised and bold) are included in the multivariable logistic regression models, variables in bold are included in the analysis.
Based upon prior evidence. AE, adverse event; FABQ, Fear-Avoidance Beliefs Questionnaire; NDI, Neck Disability Index; NP, neck pain; NRS, Numeric Rating Scale; PEL,
Patient expectations list; 95% CI, 95% confidence interval; OR, odds ratio.

4. Discussion

4.1. Main findings

We found that the occurrence of an AE during a multimodal treatment episode including MT did not influence patients' perceived recovery. Only duration of NP at baseline had prognostic value to predict recovery, whereas the remaining prognostic factors did not contribute to the model. The significant influence of duration of NP on outcome is in accordance with existing evidence; patients suffering from NP less than six weeks have better chance of recovery than patients with chronic NP (Hush et al., 2011). Adverse events do not seem to be uniquely assigned to MT. Recent studies by Paanalahti et al. and Tabell et al. showed that NSAE are commonly reported in the treatment of NP, regardless whether the intervention consisted of manipulation or other modalities. This underlines the hypothesis that the occurrence of NSAEs may be associated with patients' characteristics and less with treatment characteristics (Tabell et al., 2019; Paanalahti et al., 2014b). A systematic review by Carnes et al. also suggests that risk is inherent in all health interventions and should be weighed against patient-perceived benefit and alternative available treatments (Carnes et al., 2010).

Considering the transient and benign effects of NSAEs one could ask if the patients' benefits of adding MT to a multimodal treatment outweigh the possible discomfort of an NSAEs after treatment. Evidence from chiropractic and physiotherapeutic research on this topic is contradictory. One chiropractic study reported frequent NSAEs with none of the subjects reporting to be 'worse' or 'much worse' at the end of the study episode (Ernst, 2007). Therefore, these adverse events should in no way be misconstrued as a measure or indication of harm or be confused with (the lack of) perceived recovery. Another chiropractic study, however, showed that self-reported benign adverse events after chiropractic care for NP were associated with worse short-term outcomes (Rubinstein et al., 2008). Intense adverse events after chiropractic treatment were associated with more neck disability and clinically relevant differences at the short-term. However, there was no association between adverse events and worse outcomes at 3 months. In another chiropractic study, subjects reporting adverse reactions were less satisfied with care and less likely to have clinically meaningful improvements in pain and disability at 6, 13, and 26 weeks (Hurwitz et al., 2004). A point of discussion with regard to the conclusion of this study are the relatively small estimates and wide confidence intervals, which might also be consistent with no effect of adverse reactions on clinical outcome.

With regard to the independent variables, only about 7.7% of the total variance could be explained by our model. Although the choice of independent variables was largely in accordance with previous reports on significant predictors of outcome, the set of variables used in the present study might not have been the most relevant. It is striking that only one of the predictors identified in our study or previous studies, consistently showed an impact on GPE. Future studies should consider including other variables such as coping, illness beliefs, socio-economic factors, and lifestyle. Evidence suggests that patients' self-reported measures are stronger predictors of outcome than physical signs, therefore no physical signs were included in this study (Walton et al., 2013; De Pauw et al., 2015). Nevertheless, these physical signs might have contributed to the variance in outcome and should therefore be considered for further research.

4.2. Limitations

Although our results suggest that the occurrence of an AE during a multimodal treatment episode including MT does not influence patients' perceived recovery, this conclusion may be too simplistic. Currently, the one-in-ten rule (10 events per predictor parameter (EPP)) has generated much debate. Some authors claim that the EPP can sometimes be lowered below 10 (Vittinghoff and McCulloch, 2007). In contrast, others recommend at least 15 EPP, (Harrell, 2015) and others identify situations where at least 20 EPP or up to 50 EPP are required (Ogundimu et al., 2016; Austin and Steyerberg, 2017; Wynants et al., 2015; Van der Ploeg et al., 2014). However, a concern is that any blanket rule of thumb is too simplistic, and that the number of participants required will depend on many intricate aspects, including the magnitude of predictor effects, the overall outcome risk, the distribution of predictors, and the number of events for each category of categorical predictors (Ogundimu et al., 2016). Keeping in mind these above-mentioned criticism on the one-in-ten rule, we cannot exclude the possibility that our study was underpowered. The occurrence of NSAEs could have contributed to poor recovery but we may not have been able to demonstrate this because of the limited number of non-recovery events. Validating the results of this study in a larger sample size (with more events) and taking the intricate aspects into account, will give a better outline of the influence of NSAE on outcome.

Information on independent and dependent variables is generally captured through self-report, and this method is prone to recall or social

desirability bias. On the other hand, while measurement error in the independent variables is prone to make a model unstable, in our study the 95% CIs of the ORs are rather narrow which indicates that estimates are quite precise and the influence of this error in our study is limited.

Unfortunately, only 581 (48.6%) of participants from the total study population returned the post-treatment booklets to the research centre. The booklets included AE questionnaires as well as GPE. We applied multiple imputation techniques to the independent variables, but we chose not to impute the dependent variable GPE. To get unbiased estimates in the regression analysis, it is essential to use the dependent variable to impute values for missing data on the predictor variables but imputing the GPE-scores might lead to bias (Schafer, 1997). However, the decision not to impute GPE led to significantly less data for the analysis, leading to a possibly underpowered study.

5. Conclusion

We found that the occurrence of NSAEs did not influence recovery in patients with neck pain treated by physiotherapists with postgraduate qualifications in MT. Currently, there is no need for physiotherapists to consider NSAEs when making prognosis in these patients. But, keeping in mind the criticism on the one-in-ten rule, we cannot exclude the possibility that our study was underpowered.

Ethics approval

The Medical Ethical Committee of the Erasmus Medical Centre Rotterdam approved this study. All participants gave written informed consent before data collection began.

Source(s) of support

None.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.msksp.2022.102607.

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