THE ROLE OF ADVERSE EVENTS AFTER NAPRAPATHIC MANUAL THERAPY AS A PROGNOSTIC FACTOR

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ABSTRACT

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BACKGROUND

The primary aim of this study was to broaden the knowledge on the relationships between adverse events (AE) and recovery after Naprapathic Manual Therapy in short term and long term in low back pain and/or neck pain. Additional emphasis was on gender effect on such potential association. Manual therapy is a globally utilized, both effective and cost-effective, technique to treat low back and neck pain. AEs after manual therapy have been reported to be mainly mild and self-limiting. Previous studies have shown that AEs in patients with neck pain are not associated with worse recovery.

METHODS

The material for this study is obtained from a three-arm RCT study called Stockholm MINT trial (n=1057). There were 771 eligible patients for this prospective cohort study. AEs within 24 hours after the three first visits were measured with questionnaires and classified by inconvenience and categorised as no, mild or moderate. Outcome measure was the perceived recovery at 7 weeks and at 3 months follow-up. ORs were calculated by logistic regression by IBM SPSS Statistics 22 software. Treatment arm was included in all analyses as a covariate.

RESULTS

Genders combined ORs showed no statistically significant associations between adverse events and recovery either at 7 weeks or at 3 months follow-up. Although at seven weeks follow-up gender stratified adjusted ORs showed that men tended to have higher chance for recovery if they had had mild AEs (OR 1.46, 95% CI 0.78-2.69) while women tended to have lower chance for recovery if they had had moderate AEs (OR 0.68, 95% CI 0.41-1.14) in comparison to not having had AEs. The associations were not statistically significant though. At 3 months follow-up AEs had an effect on the chance to recovery among men. Men with mild AEs had higher chance to recover than men with no AEs (OR 2.44, 95% CI 1.24-4.80) and men with moderate AEs tended to have lower chance to recovery (OR 0.58, 95%CI 0.22-1.52). Women with mild and moderate AEs tended to have lower chance for recovery (OR 0.84, CI 0.55-140 and OR 0.68, 95% CI 0.40-1.13 respectively), but associations were not statistically significant.

CONCLUSION

This study includes both male and female neck pain and/or low back pain patients. In short term AEs after Naprapathic Manual Therapy are not prognostic factor for recovery. At long term (three months after treatment) AEs may predict better recovery for men but not for women.

Keywords: adverse event, naprapathy, manual therapy, recovery, low back pain, neck pain

TIIVISTELMÄ

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TAUSTA

Tämän tutkimuksen tarkoituksena oli selvittää sivuvaikutusten yhteyttä paranemiseen alaselkäkipu- ja/tai niskakipupotilailla naprapaattisen hoidon jälkeen sukupuolia yhdessä ja erikseen tarkastellessa. Manuaalinen terapia on maailmanlaajuisesti käytetty tehokas ja kustannustehokas hoitotekniikka alaselkä- ja niskakipuoireissa. Tutkimustulokset ovat osoittaneet manuaalisten hoitojen sivuvaikutusten olevan väliaikaisia ja voimakkuudeltaan pääsääntöisesti mietoja. Aikaisemmat tutkimukset ovat osoittaneet niskakipujen osalta, etteivät sivuvaikutukset ole yhteydessä paranemiseen.

METODIT

Tutkimusaineisto on saatu kontrolloidusta satunnaistetusta kolme hoitolinjaa sisältäneestä Stockholm MINT -tutkimuksesta (N=1057). Tähän prospektiiviseen kohorttitutkimukseen valikoitui 771 potilasta. Kolmen ensimmäisen hoitokäynnin jälkeen 24 tunnin sisällä ilmenneitä sivuvaikutuksia mitattiin kyselyllä luokitellen sivuvaikutuksen haittaavuuttaa ja kategorisoiden kolmeen ryhmään: ei, lieviä tai kohtalaisia oireita kokeneisiin. Sivuvaikutuksien yhteyttä verrattiin koettuun paranemiseen seitsemän viikon ja kolmen kuukauden kohdalla. Tilastolliset laskennat suoritettiin logistisella regressiomallilla käyttäen IBM SPSS Statistics 22 -ohjelmistoa.

TULOKSET

Sukupuolia yhdessä tarkasteltaessa ristitulosuhteet (OR) eivät osoittaneet tilastollista yhteyttä sivuvaikutusten ja paranemisen välillä seitsemän viikon eikä kolmen kuukauden kohdalla. Seitsemän viikon seurannan sukupuolen mukaan mukautetut OR:t viittasivat miehillä olevan suuremman todennäköisyyden parantua, jos heillä oli ollut lieviä sivuvaikutuksia (OR 1,46, 95 % CI 0,78 - 2,69). Naisilla todennäköisyys parantua näytti heikentyvän, jos heillä oli ollut kohtalaisia sivuvaikutuksia (OR 0,68, 95 % CI 0,41-1,14) verrattuna ei sivuvaikutuksia kokeneisiin, vaikkakin löydökset eivät olleet tilastollisesti merkitseviä. Kolmen kuukauden seurannassa sivuvaikutuksilla oli yhteys paranemiseen miehillä. Lieviä sivuvaikutuksia kokeneilla miehillä oli suurempi todennäköisyys (OR 2.44, 95 % CI 1.24-4.80) parantua kuin miehillä, joilla ei ollut ollut sivuvaikutuksia. Vastaavasti kohtalaisia sivuvaikutuksia kokeneiden miesten todennäköisyys parantua vaikutti heikommalta (OR 0.58, 95% CI 0.22-1.52). Lievä tai kohtalainen sivuvaikutusten kokeminen viittasi naisilla huonompaan paranemisen todennäköisyyteen (OR 0.84, CI 0.55-1-40 ja OR 0.68, 95% CI 0.40-1.13) ilman tilastollista merkitsevyyttä.

POHDINTA

Tutkimus sisältää sekä miehiä ja naisia ja aikaisempiin tutkimuksiin verraten niskakipu potilaiden lisäksi alaselkäkipupotilaita. Lyhyellä aikavälillä tarkasteltuna sivuvaikutukset naprapaattisen hoidon jälkeen eivät ole yhteydessä paranemiseen. Pitkällä aikavälillä , kolme kuukautta, sivuvaikutukset voivat olla edullisia miehille, mutta eivät naisille.

Avainsanat: sivuvaikutukset, naprapatia, parantuminen, alaselkäkipu, niskakipu

ABBREVIATIONS

NMT	naprapathic manual therapy
OR	Odds Ratio
MT	manual therapy
LBP	low back pain
NSLBP	non-specific low back pain
NP	neck pain
PA	physical activity
NSAID	non-steroidal anti-inflammatory drug
YLD	years lived in disability
RCT	randomized controlled trial
CNS	central nervous system

INDEX

ABSTRACT

1 INTRODUCTION 1

2 BACKGROUND 2

2.1 Pain 3

2.1.1 Manual therapy affection to pain 3

2.1.2 Prevalence of NP and LBP 4

2.1.3 Pain affection to function 5

2.1.4 Measuring pain and pain-related function 5

2.2 Adverse events 6

2.2.1 Expression and measurement of adverse events in manual therapy 7

2.2.2 Adverse events; harm or part of healing process? 8

2.3 Recovery 9

2.3.1 Prognosis of LBP and NP 10

2.3.2 Effect of manual therapy 11

2.3.3 Adverse events affection to recovery 11

2.3.4 Measuring pain related recovery 12

2.4 Naprapathic Manual Medicine 13

2.5 Aim of the study 13

3 METHODS 15

3.1 Design and study population 15

3.2 Study sample 16

3.3 Exposure-Adverse events 17

3.4 Outcome- Recovery 17

3.5 Potential confounders 17

3.7 Statistical methods 18

4 RESULTS 20

5 DISCUSSION 24

Conclusion 30

SOURCES 31

1 INTRODUCTION

Material for this thesis is obtained from a three-arm randomized controlled trial (RCT) called the Stockholm MINT-trial (the Stockholm Manual Intervention Trial). The thesis was implemented in cooperation with Karolinska Institutet under supervision of associate professor Eva Skillgate. The trial was carried out in Stockholm at the Scandinavian College of Naprapathic Manual Medicine's educational clinic. The patients participating in the trial were seeking care for neck and/or back pain at the education clinic. Trial had three treatment arms: Naprapathic manual therapy (NMT), NMT excluding spinal manipulation and NMT excluding muscle stretching. The aim of this master thesis is to broaden, through the MINT-trial, the knowledge about the role of adverse events (AEs) in recovery processes in patients with back and/or neck pain.

Global Burden of Disease Study of 2010 defined musculoskeletal diseases as second greatest cause of years spend in disability(Vos et al. 2012) with low back pain (LBP) independently more disabling than any other condition (Hoy et al. 2014a) and neck pain (NP) ranked 4th highest as years lived with disability (Hoy et al. 2014b).

Naprapathy is well established in the Scandinavian countries with 1700 Naprapaths. Soft and Connective Tissue Manipulations called Naprapathic Manual Therapy has good RCT-based evidence of effectiveness in nonspecific NP and nonspecific LBP (Skillgate et al. 2007; Skillgate 2010). Generally treating LBP by manual therapy (MT) is also cost–effective (Tsertsvadze et al. 2014).

MT as any other line of treatment seems to have AEs. AEs after MT have shown to mainly be mild and self-limiting while there are no significant differences in expression of AEs between manual therapy modalities (Senstad et al. 1997; Carlesso et al. 2010; Carnes et al. 2010b; Walker et al. 2013; Paanalahti et al. 2014b). Previous studies have shown that AEs are not associated with worse recovery at 3 months for NP patients (Hurwitz et al. 2004; Rubinstein et al. 2008b; Trott et al. 2014). Relationship with other than NP or gender related effect is still unknown.

2 BACKGROUND

LBP and NP are a huge economic burdens on families, communities and industry, LBP in order to be leading cause of activity limitation and work absence (Hoy et al. 2014a; Hoy et al. 2014b).

Estimation of NP prevalence in 12-months varies from 12% to 71 % (Haldeman et al. 2008) and chronic LBP 40% to 80% (Hayden et al. 2014). Non-specific LBP (NSLBP) seems to have a negative correlation to physical activity (PA) affecting person's ability to influence their own health through PA and by that to increase the already heavy individual and economic burden of pain (Lin et al. 2011). NP affection to PA does not seem to be as clear although it may be related to pain threshold (Cheung et al. 2013).

Pain and disability due to musculoskeletal disorders is globally increasing issue. LBP is ranked number one in years lived with disability and NP 4th highest in terms of disability as measured by YLDs (Hoy et al. 2014a; Hoy et al. 2014b). Untreated LBP and NP may be linked to diminishing ability to control the health by PA through pain affection to disability.

LBP and NP have multiple factors influencing the recovery. Systematic reviews include factors as intense of pain at baseline, younger age, comorbid LPB, sex, pain intensity and duration and general health with NP emphasis on psychological factors (Carroll et al. 2008; Lakke et al. 2009). Although the evidence of prognostic factors are conflicting, systematic review (Verkerk et al. 2012) and 1-year follow up study (Verkerk et al. 2015) have studied LPB and include variables as younger age, sex, activity of daily living, physical job demands and pain intensity at baseline which can be considered as prognostic factors depending on the outcome measure and follow-up time as well as psychological factors. On the other hand in specified pain as sciatica a systematic review by Ashworth et al. (2011) stated that age, smoking, gender, job demand nor previous sciatica have influence on recovery. A systematic review of Ebrahim et al. (2014) points out that expectations of the care seems to have high impact on the recovery as Cochrane review of Hayden et al. (2014) adds expectations of treatment being part of the recovery process.

2.1 Pain

The International Association for the Study of Pain (IASP) has defined pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP 2012). Pain can be categorised by duration, intensity and classification by its nature. Pain under six weeks is acute, between six and 12 weeks sub acute and over 12 weeks chronic. The intensity is measured by different numeric, visual and verbal scales.

LBP has international acceptance of classification of so called diagnostic-triage as spinal pathology, nerve root pain/radicular pain and nonspecific low back pain as NSLBP being the cause over 85% of cases (Airaksinen et al. 2006) and is thus the far most biggest subgroup of LBP (Hayden et al. 2014). NP categorization seems to be more complex but pain with/without radiating pain/ headache alongside serious pathologies is recognized (Childs et al. 2008).

Marras (2008) unravels the pain as describing it as a complex process which is initiated by a physical violation to the tissue through biomechanical load by compression or/and tension involving sensitivity to chemical changes in the tissue. This perception is cognised and processed in the brain influenced by person's experiences, beliefs and desires. Pain itself can be originated from injured tissue as *nociceptive pain* or from CNS as *central pain*. Pain can be divided as *peripheral pain* where nociceptive receptors of peripheral nervous system is affected or *neuropathic pain* where there is injury on the peripheral nerve and the nerve itself is the main cause of pain (Marras 2008) .

2.1.1 Manual therapy affection to pain

Marras (2008) continues that back pain is presented to rise from nerves, blood vessels, annulus fibrosus, ligaments, vertebral end plates and facets joints as well as myotendonous junction and muscles due to damage or fatigue processes. Biomechanical aspect of pain is introduced as unfavourable and uncontrolled exceeded biomechanical tissue loading which can influence the tissue tolerance and lead to damage which influence upregulation of cytokines ending up with increased nociceptor sensitivity. This onset of pain is set of complex cellular and biomechanical adaptations where stimulation of nociceptors trigger signals that

ascends to dorsal ganglion and adjacent dorsal horn interneurons and through brainstem widespread regions of cortical and subcortical CNS (Marras 2008) .

Effect of MT is often explained trough biomechanical changes. However as previously descriped pain is not just loading of tissue but complex process of CNS. MT induces stimulation of the mechanoreceptors and/or proprioceptors triggering neurophysiological changes affecting into modulation of nociceptive information, both spinal and supraspinal pathways (Bialosky et al. 2009). This relief of pain is discussed in systematic review of analgesic effect of MT (Voogt et al. 2015) which states that manual therapy increase local pressure pain thresholds in musculoskeletal pain leading to diminishing of local pain. We might assume that Naprapathic Manual Medicine practised in a described way have influence on the biomechanical loading and thus the perception of pain through complex modulation system.

2.1.2 Prevalence of NP and LBP

Prevalence of NP and LBP seems vary depending on age, definition of pain area and geographically (Fejer et al. 2006; Hoy et al. 2012). Global Burden of Disease Study of 2010 defines global point prevalence of NP 4,9 % occurring more with females at peak incidence of age 45 (Hoy et al. 2014b). Fejer et al. (2006) states one month prevalence to vary between 15-41% while one year prevalence in Scandinavia is 36% (95%, CI 22-52) and in Europe 26% (95%, CI 13-39). According to Finnish Health 2011 survey females have 41% one month prevalence of NP and men 27% (Viikari-Juntura et al. 2012).

Global Burden of Disease Study of 2010 defines global point prevalence of 9.4% for LBP highlighting in Western Europe as high as 15% (Hoy et al. 2014a). Whereas one month prevalence of LBP was estimated 23.2% and lifetime prevalence 38.9% (Hoy et al. 2012). Prevalence is higher with high-income countries compared to developing and low-income countries (Hoy et al. 2012). Gender related prevalence of LBP is greater with female individuals and at age group 40-80 years (Hoy et al. 2012). According to Finnish Health 2011 survey females have 41% one month prevalence of LBP and men 35% while in women LBP tend to common with age (Viikari-Juntura et al. 2012).

Both LBP and NP have higher prevalence with females. There are well-informed guesses for this gender difference as pain related to osteoporosis, pregnancy, individual or societal influences resulting in sex differences in the likelihood of reporting somatic symptoms etc. (Hoy et al. 2012)

2.1.3 Pain affection to function

According to Global Burden of Diseases study 2010 LBP have highest impact of years lost due to disability for men, despite that women have higher prevalence of LBP, and disability is highest between ages 35-50 (Hoy et al. 2014a). Whereas the impact of years lost due to disability in NP has greater gender effect on females and is highest in the age group of 40–45 years (Hoy et al. 2014b). Disability and physical activity has negative correlation at chronic NSLBP patients but not for acute or sub acute states of pain (Lin et al. 2011). By behavioral avoidance mechanism the decrease in physical activity can lead to increase in the level of disability (Lin et al. 2011) forming vicious circle of worsening performance. Diminishing PA may lead to lack of the patient's own ability to control the health and achieve the benefits that can be achieved by recommended level of PA. Resent longitudinal study shows that healthy life style, PA as a part of it, diminish the risk of long duration troublesome low back pain among women (Bohman et al. 2014).

2.1.4 Measuring pain and pain-related function

Measuring the pain is of primary importance in LBP and NP since the pain is important factor causing disability (Hoy et al. 2014a; Hoy et al. 2014b). The multifactorial nature of pain makes the measurements problematic and therefore great attention should be directed towards the reliable measuring instruments.

Two reviews find three commonly used pain rating scales, visual (VAS), verbal (VRS) and numerical (NRS) to be reliable, valid and suitable for clinical use with emphasis on NRS (Williamson & Hoggart 2005; Hjermstad et al. 2011). Disability can be measured using for example Roland-Morris Disability Questionnaire, Neck Pain Disability Questionnaire and Oswestry Disability Index or other self-administered questionnaires. Chronic Pain Questionnaire (CPQ) measures both pain and pain-related disability and was used in MINT-study, which this study is based on, for baseline and follow-up (Paanalahti 2014a). CPQ was

proposed by Von Korff et al (1992) for the measurement of chronic pain severity in three dimensions: persistence (duration), intensity and disability (Von Korff et al. 1992; Smith et al. 1997). This seven-piece questionnaire provides a score enabling to classify chronic pain patients into one of four hierarchical categories according to pain severity or disorder. CPQ uses NRS scale of 0–10 (0=no pain/no interference, 10=worst pain/unable to continue with these activities).

2.2 Adverse events

AEs are defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (National Institute of Health(NIH) 2006). AEs have been linked to manual therapy by saying it's *"Any unfavourable sign, symptom, or disease temporally associated with treatment, whether or not caused by the treatment"* (Pohlman et al. 2014). Although AE is part of the international clinical trial terminology and established term for this phenomenon it is also called adverse effect or symptomatic reaction or side effect or harm or unpleasant reaction. AEs are processed as new complaint or worsening of the present complaint (Eriksen et al. 2011) but definition may vary according to study. Definition of AEs is complicated as there is also consideration of AEs being severe and adverse reactions or harms not, although publications does not convey this view (Hurwitz et al. 2008).

AEs occurs in pharmacological treatments as in surgical operations and manual therapies. For example NSAIDs which are most descripted drugs for musculoskeletal disorders (Käypä hoito 2009; Atchison 2013) commonly used to assist in the management of mild-to-moderate musculoskeletal pain have well known gastrointestinal and cardiovascular effects (Atchison 2013). Injections and surgical procedures have also their AEs (Carragee et al. 2008; Öhrn et al. 2011).

Previous case reports and retrospective case studies at MT concerning cervical manual treatment may have led to over reporting of severe, irreversible AEs as vertebrobasillar artery insufficiencies leading to stroke (Carlesso et al. 2010). In examining this issue it has come to light that the increased risk of VBA after visiting chiropractor or primary care physician for neck pain is similar, and VBA related stroke risk after these visits are suggested to be related

to neck pain or headache resulting from VBA dissection (in the drogmal stage) before stroke (Cassidy et al. 2008). Study of Eriksen et al. (2011) demonstrated no severe AEs related to >5 million upper cervical manipulation administered by care-giving chiropractors (Eriksen et al. 2011).

Studies have found out that AEs are mainly short with duration and mild or moderate by their intensity, affecting up to half of the patients (Cagnie et al. 2004; Rubinstein 2008a; Carlesso et al. 2010; Carnes et al. 2010b; Eriksen et al. 2011; Paanalahti et al. 2014b).

2.2.1 Expression and measurement of adverse events in manual therapy

AEs after SMT are reported as self-limiting, transient and musculoskeletal by their nature (Cagnie et al. 2004; Hurwitz et al. 2004; Rubinstein et al. 2008b; Eriksen et al. 2011; Walker et al. 2013; Maiers et al. 2014) usually including symptoms like musculoskeletal pain, tiredness, stiffness, dizziness, radiating discomfort, headache or nausea (Senstad et al. 1997; Rubinstein 2008a; Carlesso et al. 2010). AEs are reported more common with female participants (Cagnie et al. 2004; Yin et al. 2014; Paanalahti et al. 2014b). In studies prevalence of AEs are seen to have relation to patients expectancy which is mirrored through information, consent forms or investigators behaviour (Walker et al. 2013).

Earlier studies have shown some predictability by gender. Gender specific approach shows tendency for women to have more moderate AEs than men (Paanalahti et al. 2014b). These findings are consistent with previous studies (Senstad et al. 1997; Cagnie et al. 2004) while others disagree (Hurwitz et al. 2004). The role of gender is diverse and more studied with neck pain patients.

Measurement of AEs have shown a great deal of variety although there is submitted generally accepted ideas to measure severity, duration, nature (Carnes et al. 2010a; Carlesso et al. 2011; Walker et al. 2013; Paanalahti et al. 2014b), changes in function and modification of severity (Carlesso et al. 2011). Classification to mild, moderate and major related to the measured modifications exists (Carnes et al. 2010a; Carlesso et al. 2011). Although studies have reported AEs as a negative related side effects there is need to look them broader. Questionnaires of AEs a general point of view has the basic assumption of negative nature of

AEs in isolation from the healing process. There is definition for transient AEs as benign adverse events (Senstad et al. 1997; Cagnie et al. 2004; Rubinstein et al. 2008b).

2.2.2 Adverse events; harm or part of healing process?

AEs are generally concerned, as earlier defined, as unfavourable symptoms. Whereas practitioners and researchers might have established or raised treatment-related AEs through modification based on AEs definition of NIH (2006) and Pohlman et al. (2014) there is need to see patients' perspective. Rajendran et al. (2012) found out patients describing the AEs as component of the effectiveness of treatment and natural part of the healing process. Expression of AEs was also seen as a key factor in the success and effectiveness of treatment in subjects who had previously received SMT (Rajendran et al. 2012). Negative treatment-related AEs was regarded as pain and loss of function (Carlesso et al. 2011; Rajendran et al. 2012) with impact on daily living or work (Rajendran et al. 2012). Especially loss or diminishing off function was valued more significant effect than pain itself (Carlesso et al. 2011).

Although SMT might have been considered to have more AEs, a study by Paanalahti et al (2014b) based on the same RCT as this thesis, showed that AEs in patients with LBP and/or NP treated with NMT did not differ between NMT with or without spinal manipulation. Neither did stretching as part of NMT influence the risk of AEs. Over 80% of patients seemed to have AEs ones or more, commonly soreness or stiffness in muscle or increased pain (Paanalahti et al. 2014b). Study of Senstad et al. (1997) has earlier find out that there are no associations between treatments and AEs for neck pain patients. On the contrary Hurwitz et al. (2004) don't stand along and states that cervical manipulation seems to have more AEs than mobilisation.

Systematic review of Carnes et al. (2010b) research the risk of AEs compared to exercise, drug therapy and general practitioners care. The review included 31 RCTs with spinal manipulation as one option of intervention and presents that manual therapy interventions produced more minor or moderate AEs than general practitioners care (RR 1.91), same number as exercise therapy (RR 1.04) and less than drug therapy (RR 0.05) using NSAID or amitriptyline (Carnes et al. 2010b). A systematic review estimates that treatment of lumbar disc herniations by lumbar manipulation is 37000-148 000 times safer than NSAID and

55500- 444000 times safer than surgery when comparing for example gastrointestinal or surgical AEs (Oliphant 2004).

2.3 Recovery

From the patients' point of view the diagnose may not be the "thing" but what is important is the outcome, recovery (Hurwitz et al. 2008). Expectations of recovery have many aspects (figure 1). Expectations of general recovery (return to work, duration of pain), treatment expectations (is this treatment helpful) and self-efficacy expectations (I can cope with the pain, I can return to my activities as usual) (Hayden et al. 2014). Beaton et al (2001) described resolution of "I am better" as being reflected by three different stages that could mean solution of current complaint, state of readjustment to an on going disorder, or a redefinition of what being better would be like (Beaton et al. 2001).

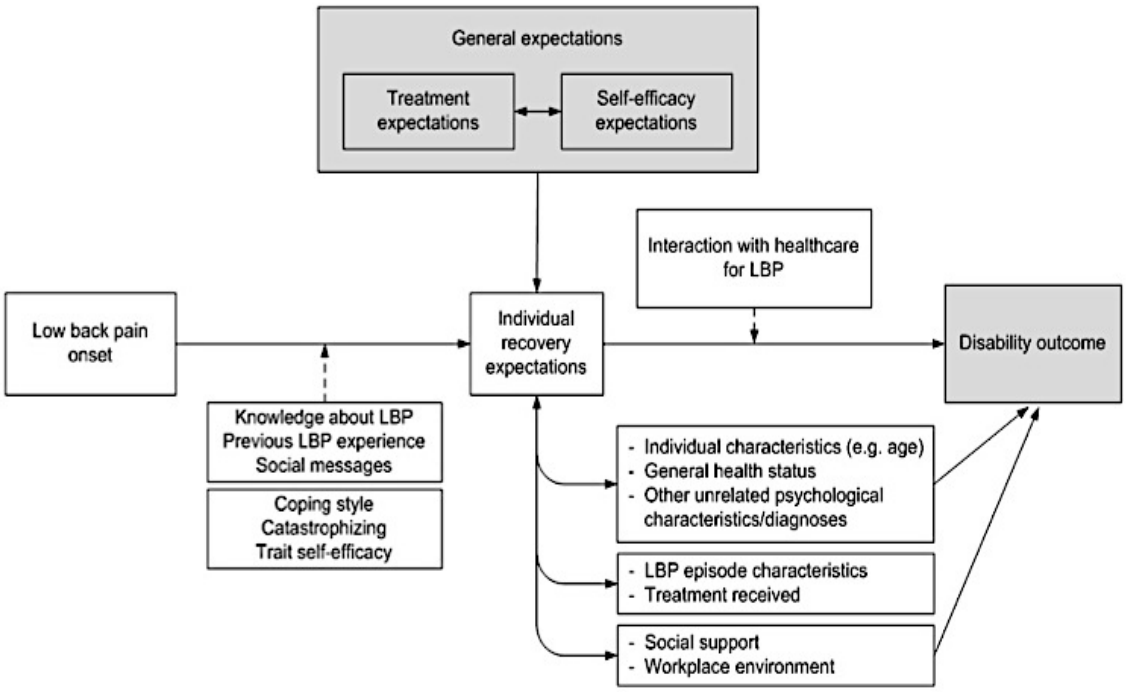

FIGURE 1. Conceptual framework of the relationship between individual recovery expectations and low back pain (LBP) disability outcomes (Hayden et al. 2014)

2.3.1 Prognosis of LBP and NP

A study of Hayden et al. (2014) states that most LBP patients recovers in few weeks although 25% to 33% continue to report LBP after one year and those develop chronic state of pain tend to show more persistent course with common habit of recurrences. Poorer recovery in LBP patients seems to be associated with factors related to the current LBP (baseline disability, radiating pain), work and social environments (colleagues, heavy physical demands) and factors shared with neck pain as older age, poor general health and psychological characteristics. Negative recovery expectations and recovery (in terms of return to work) in LBP seems to have relationship, although evidence for this is mixed (Hayden et al. 2014).

NP seems to have 50% to 80% of recurrence of pain between 1-5 years as it's submitted as multifactorial thing with poor recovery associated with older age, poorer general health, previous neck pain and negative psychological factors such as worrying and frustration (Haldeman et al. 2008). Positive prognostic factors for neck pain are optimism, self-assurance with neck pain coping style and lesser need to socialize (Haldeman et al. 2008).

A systematic review of Ebrahim et al (2014) find significant association between patient's recovery expectations and outcome and Hayden et al (2014) propose that positive expectations should be encouraged in terms of better recovery. Patient's recovery expectations can be influenced by several personal factors such as intra-personal (health status), interpersonal (family, work, healthcare provider beliefs) or system-level factors (cultural factors, employment ability) (Ebrahim et al. 2014). Experiencing AEs might have effect on treatment-expectations and thus recovery. Therefore Rajendar et al (2012) propose adequate informing prior the treatment concerning possible post-treatment pain, stiffness or tiredness as it seems to affect the perception and expectations of treatment itself and possible AEs. Prior informing could support reduction of symptoms and support positive health outcomes together with quality care (Rajendran et al. 2012).

Recovery seems to differ between genders. It seems that leisure time physical activity is related to greater chance to recover from LBP (Bohman et al. 2013) and NP (Rasmussen-Barr et al. 2013) for women. Greater recovery is related to greater leisure time PA. As earlier

stated women are more affected by LBP and NP. They also have more recurrent LBP and worse prognosis than men (Chenot et al. 2008).

2.3.2 Effect of manual therapy

Manual therapy is one, non-surgical way to assessing, diagnosing and treatment of various musculoskeletal symptoms and pain using practitioner's hands and fingers. MT is widely used technique by many professions (naprapathy, chiropractors, osteopaths etc.), which consisted of multiple techniques (manipulation, mobilization, stretching, connective tissue treatment etc.).

According to systematic reviews manual therapy is both effective (Furlan et al. 2011; Hidalgo et al. 2014) and cost-effective (Tsertsvadze et al. 2014) treatment of LBP and NP, although the cost-effectiveness of NP is not consistent across studies. Effectiveness is even better if NSLBP patients are sub classified (Fersum 2010). Combination of manual therapy and exercise seems to have great effect on pain and function for NP states (Hurwitz et al. 2008; Miller et al. 2010).

There is good RCT-based evidence of NMT effectiveness in non-specific NP and NSLBP (Skillgate et al. 2007; Skillgate 2010) as well as cost effectiveness (Lilje et al. 2014). Use of MT is recommended in the United States, Great Britain, Canada, and the Netherland (Tsertsvadze et al. 2014) and clinical practice guidelines for acute NSLBP (van Tulder et al. 2006; Delitto et al. 2012), chronic NSLBP (Airaksinen et al. 2006; Delitto et al. 2012), acute and chronic NP (Childs et al. 2008; Bryans et al. 2014). Instead of this previously presented vast studies recommendations of SMT is ambiguous in non-specific acute or chronic LBP in Finland (Käypä hoito 2014).

2.3.3 Adverse events affection to recovery

Manual therapy interventions seem to have AEs as described but at the same time studies have shown good recovery outcomes (Rubinstein et al. 2007; Eriksen et al. 2011). Although study of Hurwitz et al (2004) find out that patients reporting AEs were less satisfied with care, perceived less improvement to their neck symptom and had more pain and disability during

follow-up compared to patients who didn't report any AE's when AEs were more likely in manipulation than mobilisation group (Hurwitz et al. 2004).

Trott et al. (2014) brings out that MT after new onset of NP even associated with minor AEs or relapses during treatment are not associated with delayed recovery (Trott et al. 2014). Although intense AEs are associated with more disabling NP and have clinically significant short-term effect on recovery there are no association with AEs and worse recovery after three months (Rubinstein et al. 2008b). AEs after naprapathic manual therapy have been reported in two previous studies but their affection to recovery has not been published (Skillgate et al. 2007; Paanalahti et al. 2014b).

2.3.4 Measuring pain related recovery

Effectiveness of treatment can be defined by its outcomes. Recovery as an outcome have multiple measurement options and multiple options have been used (Kamper et al. 2011; Chapman et al. 2011). Hayden et al. (2014) propound factors as pain, functional limitations and return to work while Chapman et al. (2011) add quality of life, psychosocial factors and preference-based measurements for cost-effectiveness. Recovery measurement can also be subjective, patient-specific approach, sensation of recovery (Rubinstein et al. 2008b; Paanalahti et al. 2014b). Patient-specific approach asking perceived recovery has been used in previous studies (6-point Likert scale: "completely improved," "much better," "somewhat better," "unchanged," "somewhat worse," "much worse" as dichotomised the variables; "completely improved" and "much better" as recovered) (Rubinstein et al. 2007; Rubinstein et al. 2008b; Paanalahti 2014a).

Self-reported rate of recovery seems to correlate with changes in pain and disability scores during MT (O'Halloran et al. 2013). Farrar et al. (2001) find out that with chronic pain patients clinically important change in pain as 'much improved' or 'very much improved' is related to a 30% or 2 point reduction in pain, respectively. There are also establishment for meaningful changes in LBP as minimal important change of at least 2 point decrease (NRS) or 30% improvement compared to baseline (Farrar et al. 2001; Ostelo et al. 2008). Verker et al. (2015) considered pain scores below one as recovered. Eriksen (2011) define recovery as NRS<3 and current pain <10% of pain in baseline. Trott (2014) defines recovery as NRS<1.

2.4 Naprapathic Manual Medicine

Finnish Naprapathic Association defines Naprapathy as a system for specific examination, diagnostics, manual treatment and rehabilitation of pain and dysfunction in the musculoskeletal system. The therapy is aimed at restoring function, through treatment, which are believed to cause pain and disability.

Manual therapy provided by naprapaths is called Soft and Connective Tissue Manipulations (SCTM), and is a combination of manual techniques as spinal manipulation/mobilization, stretching and massage to restore function of the connective tissue, muscle- and neural tissues within or surrounding the spine and other joints that are thought to be common causes to these pain conditions (Skillgate et al. 2007). Naprapathy is well established in the Scandinavian countries with 1700 Naprapaths. The first Naprapathic College outside the United States was founded in Sweden in 1970 and education started in Finland in 2003. First Naprapaths came to Finland in 1975.

Naprapathy was originally initiated in 1907 in the United States by Dr. Oakley Smith. Oakley stated the term ”Ligatight” to describe impairment nerve function, as cause of pain, by the contraction of the connective tissue through which the nerve passes (Oakley 1923). Naprapathy, which literally means “to correct the cause,” is a health profession characterized by viewing the neuromusculoskeletal system as a whole.

Naprapath has been a registered health profession in Finland since 1994 and is controlled by National Supervisory Authority for Welfare and Health. Two randomized controlled studies have been suggested as naprapathy to be an effective treatment for NSLBP and NP (Skillgate et al. 2007; Skillgate 2010). Naprapathy has been suggested to be cost effective treatment for orthopaedic outpatients with disorders unlikely to benefit from surgery (Lilje 2010; Lilje et al. 2014)

2.5 Aim of the study

Among manual therapists there has been unspoken knowledge of doctors’ assumption of AEs as decreasing factor for prognosis. At the same time treatment induced cascade of neurophysiological responses (Bialosky et al. 2009) of the symptomatic tissues in order to

relief the pain may temporarily affect the perception of pain through the biomechanical changes in tissue loading.

The primary aim of this master thesis is to broaden the knowledge and relationship between AEs and recovery after Naprapathic Manual Therapy in short term (seven weeks) and long term (three months). Previous studies have been shown statistical significant differences between males and females according to occurrence of AEs (Cagnie et al. 2004; Yin et al. 2014; Paanalahti et al. 2014b). Through this knowledge additional aim was to compare gender oriented effect of AEs to recovery.

3 METHODS

3.1 Design and study population

This study was based on a randomized controlled trial (RCT), the Stockholm Manual Intervention Trial (MINT). The trial had the main aim to compare three different treatment arms within NMT and also to study the occurrence of AEs between the treatment arms. Patients with back and/or neck pain seeking care at the educational clinic of the Scandinavian College of Naprapathic Manual Medicine in Stockholm, Sweden, were asked to participate in the study. Inclusion criteria were age 18-65, and no visits to the clinic during the previous month. Exclusion criteria were; 1) not mastering Swedish language well enough to independently complete the questionnaire, 2) low pain score (<2 on an 11-point numerical rating scale between 0-10) reporting present pain and worst pain the past four weeks, 3) pregnancy, 4) current or past cancer, 5) receiving treatment by a chiropractor, osteopath, physiotherapist or naprapath during the past month for the current complaint, 6) duration of current complaint less than one week, 7) demanding or refusing spinal manipulation or stretching, 8) contraindication for spinal manipulation according to the Swedish Board of Social Welfare, 9) no indication for spinal manipulation in the area seeking care for, 10) red flags, 11) specific diagnoses (for example ankylosing spondylitis, spinal stenosis, rheumatoid arthritis), 12) sick leave due to planned/completed surgery for neck and/or back. Study participants were provided maximum of six treatment sessions within six weeks by students in the seventh semester of a total of eight, under supervision of experienced registered naprapaths.

The treatment arms were; 1) manual therapy techniques, (a combination of spinal manipulation, mobilization, muscle stretching and massage, 2) manual therapy techniques excluding spinal manipulation, and 3) manual therapy techniques excluding stretching. At the first visit, before being assigned to a certain treatment, the participants filled out a baseline questionnaire including questions about lifestyle factors, previous problems, pain intensity, pain related disability, expectations of recovery etc. At all return visits to the clinic the AEs within 24 hours after previous visit were measured with questionnaires. Follow-ups were

performed by questionnaires sent to their home or their email, at seven weeks, three, six and twelve months after baseline.

3.2 Study sample

Study sample was selected among the participants in the Stockholm MINT study from those who had at least three treatments and had answered adverse events questionnaire from the first three visits (n=771). Drop outs, 29 at seven weeks and 31 at three months, didn't answer the follow-up questionnaire. Flowchart of inclusion in the study is displayed in (figure 2).

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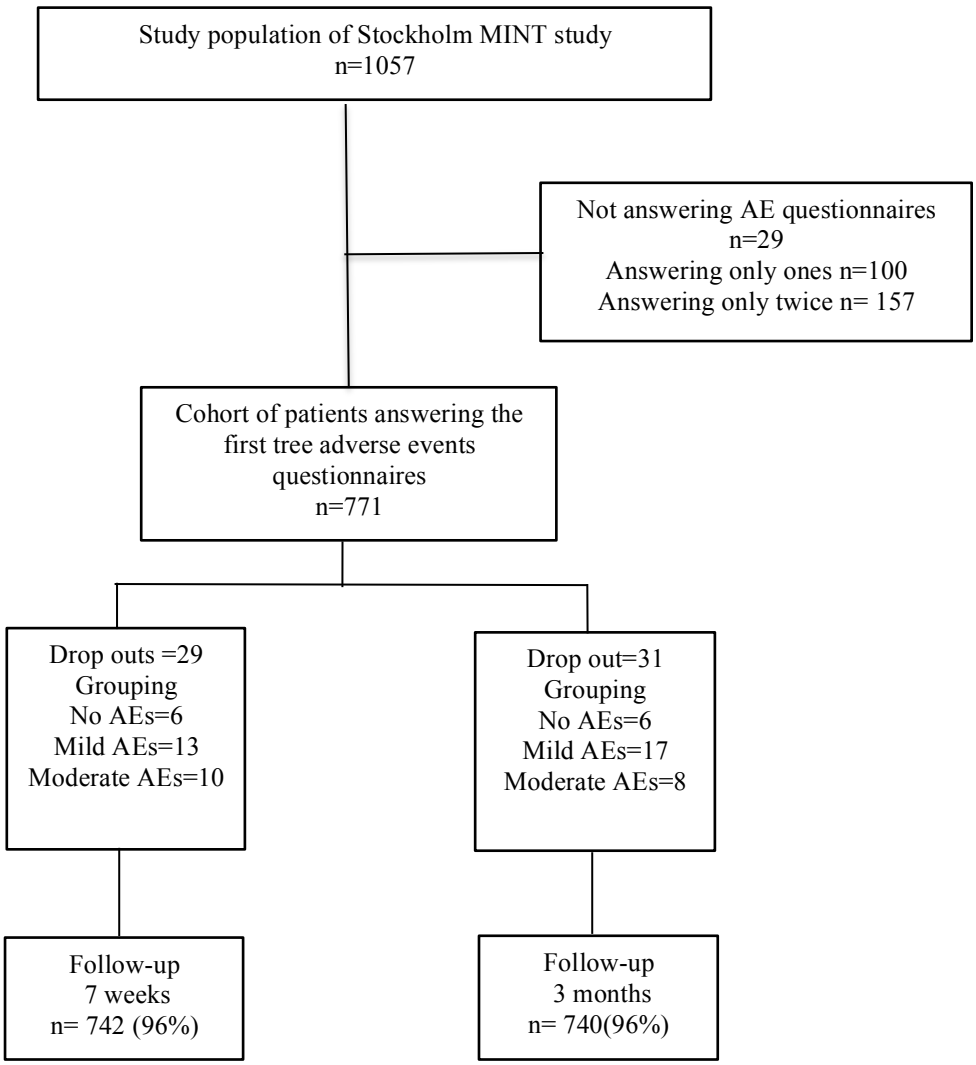

FIGURE 2. Flowchart of inclusion process for the study.

3.3 Exposure-Adverse events

AEs was used as the exposure. Each AE questionnaire included eight questions concerning if participant have been bothered by any AEs within 24 hours after treatment. AEs were defined as 1)tiredness 2)soreness in muscles 3)stiffness 4)increased pain 5)nausea 6)headache 7)dizziness or 8) "other". Bothersomeness was measured by an 11-point numerical rating scale (NRS) from 0–10 (0 = had not bothered them at all and 10 = had bothered them in the worst possible way). If patient had not experienced AE it was classified as zero. One, highest value of bothersomeness from eight possible AEs in scale of zero to 10 from each three questionnaire was included into the count of the mean of the three sessions. AEs were categorized into three levels, using whole numbers (integers), according to severity of bothersomeness as no(<1), mild(1-3) or moderate-(≥4). A previous study from Paanalahti et al. (2014b) based on the same MINT-trial have used similar classification as ≤3 minor and above 3 as moderate.

3.4 Outcome- Recovery

The outcome was measured with a follow-up questionnaire that includes question of perceived recovery measured by Global Perceived Recovery Question (6-point Likert scale). The question was; "Which of the following statements describes how you experience the changes of your disorder in the neck or/and back since your joined the study". Answering options were; "Feel no pain at all and neither other disorder from your neck or/and back", "Is considerably better", "Is slightly better", "No Improvement", "Is slightly worse", "Is considerably worse". Answers "Feel no pain at all and neither other disorder from your neck or/and back" and "Is considerably better" were defined as recovered. Farrar et al. (2001) defined a clinically important change in pain as 'much improved' or 'very much improved' using the Global Rating Scale to be related to a 30% reduction in pain. Similar definitions and 6-point rating scale has been used in several studies (Farrar et al. 2001; Rubinstein et al. 2007; Rubinstein et al. 2008b; Paanalahti 2014a).

3.5 Potential confounders

Potential confounding factors were the factors reported in table 1identified through theoretical and empirical considerations and data available from baseline questionnaire. Rothman (2012)

says that confounders must be associated with AEs and need to have effect on recovery. This study is based on randomised controlled study which is part of controlling confounding. This design was not used in this thesis- as the study population was considered as one cohort. To control the confounders statistically there is chance of isolation, stratification into specific age groups and comparison of risk or odds ratios (logistic regression) or to compare -2 Log likelihood values of crude and adjusted models. Confounding is a causal concept and cannot be described neither in terms of correlations nor associations (Rothman 2012, 33, 142 and 218-219).

3.7 Statistical methods

Descriptive statistics were used to summarize baseline characteristics and describe the frequency. Several baseline variables were dichotomized and categorised suitable for analyses. Duration of pain was dichotomized to acute/sub acute (≤3 months) and chronic (>3moths). The pain at the baseline was mean of three questions about pain right now, worst pain in the last four weeks and average pain of the last four weeks calculated from 11 point NRS from 0–10 (0 = no pain and 10 = worse possible pain). Disability at the baseline was also the mean of three questions about how much has the pain hindered your daily activities in the last four weeks, how much pain has affected your social activities in the last four weeks and how much your pain has interfered your work in the last four weeks calculated from 11 NRS from 0-10 (0 = had no effect to function and 10 = impossible to perform activities). General health categorization 1) excellent 2) very good 3) good 4) fair and 5) poor was modified as good or better (1, 2 and 3), fair and poor.

Recovery expectations was measured as patients judged how likely is it that there are no symptoms in seven weeks at 11 point scale as 0=not at all likely and 10=very likely. Distress was defined asking how much of the time patient has felt gloomy and sad in the last four weeks on six point scale (1=all the time and 6=not at all).

Logistic regression modelling was used to determine odds ratios (ORs) and 95% confidence intervals (CI 95%) for AEs affection to perceived recovery. If the 95% CI for the OR contains 1.0, the association were not significant at the 0.05 level. Each potential confounder was tested by adding it to crude model one at time. If adjusted model changed the point estimate 10% or more confounding was considered present and it was added to the model (Rothman

2012, 141). Treatment arms of original RCT study were included as a covariate in all models to adjust for potential differences in treatment effect. Statistical analysis was performed using IBM SPSS version 22 for Mac.

4 RESULTS

Table 1 shows the patients characteristics stratified by bothersomeness of AEs. The study population has mean age of 36 and 71 % are women. Chronic pain was reported by 37% of the patients, average pain as five (NRS 0-10) and recovery expectations as 6 (NRS 0-10). General health was reported at least good by 95% of patients. Distress as psychological factor and recovery expectations are equally divided between AE modalities.

AEs with main complaint of soreness in muscle were obtained in 76% of patients after three visits. At treatments arms no-manipulation group was the least expressed in no-AEs group and most expressed in mild-AEs group. Women were over-represented at moderate-AE group while men were over-represented at no-AEs group. No serious AEs were reported in the main study.

Seven weeks follow-up. Table 2 presents the proportions of recovered women and men at the seven week follow-up stratified by bothersomeness of AE. The associations between AE and the chance to recover at seven weeks follow-up are presented in Table 3. When analysing both gender combined and men separately recovery expectations turned out to be a confounder at seven weeks follow-up and was included in the adjusted models. Treatment arm was included in all analyses as a design variable. There were no clear associations when men and women were analysed together.

Men tend to have higher chance for recovery if they have had mild AEs (OR 1.46, 95% CI 0.78-2.69) while women tend to have lower chance for recovery if they have had moderate AEs (OR 0.68, 95% CI 0.41-1.14) in comparison to not having had AEs. None of the associations were statistically significant though.

TABLE 1. Baseline characters of study participants stratified by adverse events after first three visit's mean (n=771)

	All		No AEs (NRS <1) (n=182, 24%)		Mild AEs (NRS 1-3) (n=401, 52%)		Moderate EAs (NRS ≥4) (n=188, 24%)	
Characteristics	No.	%	No.	%	No.	%	No.	%
Mean age	36(12)		36(12)		36(12)		36(12)	
Gender								
• Women	545	71	106	58	285	71	154	82
• Men	226	29	76	42	116	29	34	18
Painful area								
• Back	255	33	79	43	123	31	53	28
• Neck	422	55	83	46	219	55	120	64
• Back/Neck	94	12	20	11	59	15	15	8
Duration of pain								
• Acute/sub acute (≤ 3 months)	488	63	113	62	260	65	115	61
• Chronic (>3 months)	283	37	69	32	141	35	73	39
Previous similar complaints	599	78	137	75	312	78	150	80
Pain at baseline (SD)[a]	771		5(2)		5(2)		6(2)	
Disability at baseline (SD)[b]	771		2(2)		2(2)		3(2)	
Recovery expectations (SD)[c]	771		6(3)		6(3)		6(3)	
General health								
• Good or better	731	95	173	95	379	95	179	95
• Fair	40	5	9	5	22	6	8	4.5
• Poor	1	<1	0	0	0	0	1	0.5
Education								
• Elementary school 1-9 years	26	3	8	4	10	3	8	4
• High school 10-12 y	268	35	70	39	128	32	70	37
• University 13-15 y	375	49	80	44	205	51	59	48
• Higher academic education ≥16	102	13	24	13	58	15	20	11
Distress (SD)[d]			5(1)		5(1)		5(1)	
Daily smoking	105	14	18	10	56	14	31	17
RCT group								
• Naprapathic manual therapy	244	32	62	34	121	30	61	32
• NMT- no manipulation	265	34	53	29	148	37	64	34
• NMT- no stretching	262	34	67	37	132	33	63	34

[a]Average of three questions from (0 = no pain and 10 = worse possible pain)how strong is the pain right now, intensity of the worst pain in the last four weeks and average of the last four weeks.
[b]Average of three questions from (0 = had no effect to function and 10 = impossible to perform activities) affection to function in the last four weeks, affection to social activities and affection to work.
[c] Expectation of asymptomatic pain area in seven weeks(0=not at all and 10=very likely).
[d] Have you felt gloomy and sad in the last four weeks(1=all the time and 6=not at all).

TABLE 2. Expression of recovered participants by gender at seven weeks follow-up stratified by adverse events. (N=742)

	All		No AEs (NRS <1)		Mild AEs (NRS 1-3)		Moderate AEs (NRS ≥4)	
	n=392(53%)		n= 94(53%)		n=212(55%)		n=86(48%)	
Characteristics	No.	%	No.	%	No.	%	No.	%
• Recovered women	280	53	59	57	151	55	70	48
• Recovered men	112	52	35	47	61	54	16	50

TABLE 3. Associations between adverse events and perceived recovery as chance to recover at seven weeks follow-up presented as Odds Rate (OR) and 95% confidence intervals (CI). n=742

	All			**Men**			**Women**	
	OR (95% CI)			**OR(95% CI)**			**OR(95% CI)**	
Adverse Events	n(%)	Crude[a]	Adjusted[b]	n(%)	Crude[a]	Adjusted[c]	n(%)	Crude[a]
No	176 (24)	1.0 (ref.)	1.0 (ref.)	74 (34)	1.0 (ref.)	1.0 (ref.)	102(19)	1.0 (ref.)
Mild	388 (52)	1.05(0.74-1.50)	1.14 (0.79-1.64)	111(51)	1.36 (0.76-2.46)	1.46(0.78-2.69)	277(53)	0.88 (0.56-1.39)
Moderate	178 (24)	0.82(0.54-1.24)	0.92 (0.60-1.41)	32(15)	1.13 (0.49-2.59)	1.25(0.53-2.93)	146(28)	0.68 (0.41-1.14)

[a]Treatment arm included in analysis
[b]Adjusted for treatment arm and recovery expectations
[c]Adjusted for treatment arm and recovery expectations

Three months follow-up. Table 4 presents the proportions of recovered women and men at three months follow-up stratified by intensity of AE. The associations between AE and the chance to recover at three months follow-up are presented at Table 5. When analysing both genders combined recovery expectations turned out to be confounder for mild and moderate AEs and was included in the adjusted models. Treatment arm was included in all analyses as a design variable. There were no clear associations between AEs and chance to recover in the gender combined analyses.

Distress, disability at baseline and pain duration were confounders in moderate AEs and pain location in mild AEs for men. For women pain at baseline was a confounder in moderate AEs group. Women with mild and moderate AEs tend to have lower chance for recovery than women with no AEs (OR 0.84, 95% CI 0.55-1.40 and OR 0.68, 95% CI 0.40-1.13 respectively), but the associations were not statistically significant. Men with mild AEs have higher chance to recover than men with no AEs (OR 2.44, 95% CI 1.24-4.80) and men with moderate AEs tend to have a lower but not statistically significant chance to recover (OR 0.58, 95% CI 0.22-1.52).

TABLE 4. Expression of recovered patients by gender at three months follow-up stratified by adverse events (n=740).

	All		No AEs (NRS <1)		Mild AEs (NRS 1-3)		Moderate AEs (NRS ≥4)	
	n=380(51%)		n= 93(53%)		n=210(55%)		n=77(42%)	
Characteristics	No.	%	No.	%	No.	%	No.	%
• Recovered women	267	48	59	57	143	53	65	44
• Recovered men	113	51	34	47	67	60	12	36

TABLE 5. Associations between adverse events and perceived recovery as chance to recover at three months follow-up presented as Odds Rate (OR) and 95% confidence intervals (CI) (n=740).

	All			**Men**			**Women**		
	OR (95% CI)			**OR(95% CI)**			**OR(95% CI)**		
Adverse Events	n(%)	Crude[a]	Adjusted[b]	n(%)	Crude[a]	Adjusted[c]	n(%)	Crude[a]	Adjusted[d]
No	176(24)	1.0 (ref.)	1.0 (ref.)	73(34)	1.0 (ref.)	1.0 (ref.)	103(19)	1.0 (ref.)	1.0 (ref.)
Mild	384(52)	1.08(0.75-1.54)	1.19 (0.82-1.72)	112(51)	1.72 (0.95-1.12)	2.44(1.24-4.80)	272(53)	0.83 (0.53-1.91)	0.84 (0.55-1.40)
Moderate	180(24)	0.67(0.44-1.01)	0.76 (0.50-1.18)	33(15)	0.66 (0.28-1.55)	0.58(0.22-1.52)	147(28)	0.60 (0.34-0.99)	0.68 (0.40-1.13)

[a]Treatment arm included in analysis
[b]Adjusted for treatment arm and recovery expectations
[c]Mild AEs; Adjusted for treatment arm, recovery expectations and pain location.
[c]Moderate AEs; Adjusted for treatment arm and recovery expectations, distress, disability at baseline and pain duration.
[d]Adjusted for treatment arm and pain at baseline (confounder for women in moderate AEs)

5 DISCUSSION

The primary aim of this study was to investigate AEs after Naprapathic Manual Therapy as a prognostic factor at seven weeks and three months follow-up. In addition, men and women were compared regarding to the chance to recover depending on the intensity of AEs. This study was based on randomized controlled trial comparing prevalence of AEs within three treatment arms demonstrating no difference within treatment arms in overall but effect for women (Paanalahti et al. 2014b). Through this knowledge treatment arms were included in all analysis and gender were regarded separately.

Augment to previous studies this study includes both NP and/or LBP patients while previous studies have largely focused on NP patients (Hurwitz et al. 2004; Rubinstein et al. 2008b; Trott et al. 2014). Addition to former NP based approaches this study also includes gender based comparison. Similar to previous studies baseline values showed women to occupy patients' gender distribution (Hurwitz et al. 2004; Rubinstein et al. 2008b; Trott et al. 2014).

At least 81% of women had had some intensity of AEs while the number for men was 66%. NP as main complaint was present in 55% of cases and LBP 33%. The rest had equally bad pain in neck and back. In this study 37% were evaluated as chronic pain patients, proportions divided equally between genders. Similar complaints had previously experienced 78% of all patients.

Seven weeks follow-up. AEs weren't prognostic factor for patients seeking relief for NP and/or LBP. This is not consisted with the study of Rubinstein et al. (2008b) demonstrating AEs to be associated with worse recovery for NP patients. Fifty-three percent of patients felt they were recovered and distributions were fairly even divided by AEs as no-AEs 53%, mild-AEs 55% and moderate-AEs 48%.

Gender stratified proportion of recovered patients showed to be fairly equal. There seems to be a tendency for men to benefit from both mild and moderate AEs while the effect was opposite for women. Despite this observations AEs did not have any statistical significance at seven weeks follow-up.

Recovery expectations turn out to be the only confounding factor for gender combined and for men and were added to adjusted ORs. Although confounding doesn't mean causality there is well known importance of expectations of recovery as prognostic factor (Ebrahim et al. 2014; Hayden et al. 2014)

Three months follow-up. AEs were not a prognostic factor when both gender were analysed together, which is consistent with previous studies (Hurwitz et al. 2004; Rubinstein et al. 2008b; Trott et al. 2014). Overall recovery at three months had changed from seven weeks 53% to 3-months 51%. No AEs and mild AEs group showed the same tendency as in seven weeks follow-up. Proportion of recovered in moderate AEs group was lower (42%) compared to seven weeks (48%).

Gender stratified analyse showed significally better chance to recover (OR 2.44, 95% CI 1.24-4.80) for men who have had mild AEs in comparison to men with no AEs. Crude analysis, including treatment arms, showed a decrease chance to recovery (OR 0.60, 95% CI 0.34-0.99) for women who had had moderate AEs, although adjusted OR (OR 0.68, 95% CI 0.40-1.13) was not statistically significance.

Strengths and limitations. This study was based on randomized controlled trial (n=1057) and had 771 eligible patients. Data for strengths and limitations of research in which this study is based on are available at Paanalahti et al. (2014b). Absolute strengths of this study are the proportion of patients, the careful management of confounders and the great respond rate. Confounding analysed in this study were identified through theoretical and empirical considerations available from baseline questionnaire. A limitation is that there might be residual and unmeasured confounding biasing the results in this study. There were no knowledge of patients use of medication, possible sport or work related traumas or overloads or changes in general health (pregnancy, infections etc.). All patients were also volunteers and were already seeking help for their complaints. Thus they may have positive expectations for NMT. Although some of them have had naprapathic treatment before and may have been disappointed with the treatment arm they were randomized to which could have effect on their answers. As we know multiple factors from patho-anatomical to neuro-physiological (O'Sullivan 2005) and cognitive-behavioural (Vibe Fersum et al. 2013) may have effect on recovery and thus the range of confounding are wide and can never be wall-to-wall.

At therapeutic point of view perceived recovery as outcome value speaks out the most important value, the patient's own experience. Perceived recovery is also represented to increase the relevance of information from trials to practice (Fischer et al. 1999) and is reliable assessments of current health status in people with musculoskeletal disorders (Kamper et al. 2010).

The high respond rate could be explained by intense of follow-up by letters, e-mail or by phone. Some of the patients were familiar with NMT and recognized the need for study, which emphasized the patients' motivation. Patients were given one free visit for participation. Other expenses including treatment they paid themselves.

AEs were categorized into no, mild and moderate demonstrating the current concept of Carnes et al. (2010a) following the same NRS values than previous study of (Walker et al. 2013). Also bothersome AEs (NRS >7) were valued but low proportion of patients (3%) reaching up to that level meant that the group was too small for statistical processing. Choosing highest value from each three questionnaire and counting of the mean of the three sessions does not take into account the potential cumulative effect of multiple AEs in single session. Taking account the first three sessions combined doesn't resolve if there is specific effect of some of the individual sessions. Although Senstad et al. (1997) find out that AEs are reduced as number of session exceed four. At therapeutic point of view important factor is progress between treatments and main outcome. Even if the patient have had AEs there also should be outcomes suggesting progress and positive thoughts.

Adverse events. What is the meaning of AEs and are they part of the healing process? It has been submitted that AEs are common and that most were of mild intensity. These findings are in line with previous studies (Cagnie et al. 2004; Rubinstein 2008a; Carlesso et al. 2010; Carnes et al. 2010b; Eriksen et al. 2011; Paanalahti et al. 2014b). As systematic review of Carnes et al. (2010b) demonstrated that manual therapy produces same amount of AEs as physical exercise and less than drug therapy.

We should ask are AEs, although they aren't outcomes to prefer, part of healing process. Side effects, or AEs, concerning physical exercise are part of adaptive processes that cardiovascular and musculoskeletal systems go through to reach the outcome, better health or physical improvement. As Rajendar et al. (2012) has represented expression of AEs has also

seen as a key factor in the success and effectiveness of treatment in subjects who had previously received SMT. How could we define that AEs are normal and/or beneficial part of outcome? Are there benign and bad AEs separately when severe AEs are outlined? Definition of benign AEs is not supported by the view of Cook et al. (2012) where they defines in mouth of Maitland and Hahne that "*primary and simplistic principle of manual therapy decision making suggests that if a patient improves after application of a passive technique then that patient is a candidate for a manual therapy treatment regimen, whereas if the patient worsens, then the technique should be altered or abandoned*."

Is Cook right? This study has shown that it is not that simple. Occurrence of LBP or NP doesn't usually fit in traditional "disease" model or have clinically identified diagnosis. As earlier discussed, pain is complex and wide concept. Biomechanical model consist of compression and tension of excessive loading of tissues leading to "fatigue failure" or "elastic limit". The border between the tissue strengthening and overload is subtle. Some tissues like intervertebral discs and ligaments, compared to muscles, responds slowly and perhaps incompletely to biomechanical chances (Adams et al. 2006). This responding could happen slowly during the pain generating mechanism. After biomechanical unloading procedures done by NMT and conditioning the respond could also be slow. Using NMT and/or exercise produces forces interacting with motor and sensory control of entire spine and related joints. This effect loads sensitive nerve endings found in muscle and tendons providing proprioceptive information including pain (Indahl & Holm 2007). An alteration in loading of spine from "pain state" to "relief" needs readjustments in sensory-motor control and environment around sensory nerves (Indahl & Holm 2007). This could be the reason why AEs occur.

Recovery. The pain itself, as has been described, is a multidimensional event from stimulus to the perception. Women in general seem to experience more LBP and NP and may thus seek more palliative treatments such as naprapathy. In examination of pain the biomechanical model would fit for both gender but it would be essential to find the assumptions of sustaining beliefs behind pain and ways of manage them. Possibly gender specific.

Manual therapy causes changes in pain sensation (Bialosky et al. 2009; Voogt et al. 2015) affecting the healing process, enabling among other to do therapeutic exercises recommended both NP and LBP. In the light of the scientific study, treatment effects and treatment

indications cannot be justified either by permanent changes in joint positions (Goode et al. 2008) or adequate motion palpation (Seffinger et al. 2004, Goode et al. 2008). This vision is not shared with manual therapist and not even with some scientist with practical knowledge of MT. As discussed earlier effect of MT is the sum of many parts more than just biomechanics. Perhaps permanent changes in specific joint positions is not relevant but the overall change, helped by NMT, resulting in the alleviation of pain and therefore better postural management and a more favourable tissue loading.

As there are multifactorial models to approach LBP from patho-anatomical to biopsychosocial etc. point of view there are also many ways to look at the pathways of MT. In the knowledge of this vast variety of underlying factors we should consider recovery as experience. As an experience of individuals' own presumption how the current state of LBP or NP is felt. This study started from the premise in which the patient's perceived recovery was more important than the measured change in pain. From the patient's perspective, the question is easy to understand and it allows them to rate the current state of recovery that is most important to them. After all there are established several resolutions for recovery as Beaton (2011) has stated. Hayden et al. (2014) stated factors as baseline disability and psychological characteristics to be associated with poorer recovery. These factors were confounding in 3-months follow-up and should be studied for potential association.

The improvement seems to be gender-neutral although it wasn't estimated in this study. Previous studies have showed gender specific differences in prognosis of LBP for women to have lower chance to recovery (Chenot et al. 2008; Bohman et al. 2013). Psychological factors, pain at baseline and pain in other parts of the body are linked to increased utilization of healthcare services for women (Chenot et al. 2008) and might be prognostic factors. Pain at baseline was also confounder at 3-months follow-up for women and should therefore be examined more.

At 3-months follow-up recovery expectations were also confounding factor for both gender combined and for men as in seven weeks follow-up. Recovery expectations has shown to be an important prognostic factor (Ebrahim et al. 2014) and patients should be encourage with positive taught (Hayden et al. 2014). Three months follow up adds pain location, distress, disability at baseline and pain duration for men and pain at baseline for women as confounding factor Table 5. Although confound is not causal pathway to recovery this study

suggest that they should be studied individually as prognostic factor. The crude analysis presupposing treatment arms may having effect on recovery for women needs more research.

Meaning in healthcare. The results of this study is in line with the results of previous studies according to which the AEs are not related to worse outcome in the context of the results of the three-month period. In addition, the study showed that a short-term recovery is not related to AEs reported in the course of treatment process. This observation together with treatment outcomes and cost-effectiveness of Naprapathic Manual Therapy supports the use of manual therapy as integrated treatment from of LBP and NP. In addition, this confirms the NMT to be integrated in the health and social system even broader scale.

By integrating into public healthcare systems skilled and authorities supervised manual therapy professionals such as naprapaths the most effective way to treat LBP and NP patients could be reached. In Finland, the current sickness compensation system does not control the contents of treatments and therefore there is no guarantee how the state-controlled compensation policy is issued in connection with evidence based best practise treatment or to European guidelines and / or Finnish guidelines. Although MT is widely used practise in field of NP and LBP there are just a few or practically none MT experts in processes creating Finnish treatment recommendations for LBP or NP.

General discussion. Interventions that reduce the prevalence of LBP and NP would lead to improvements on a public health level and individually and potentially have large economic benefits. Benefits of MT are obvious and it is a widely used format all over the world to treat musculoskeletal disorders. Combined with adequate exercise, postural and movement control, excellent results have been achieved. At the societal level the benefits to save sick days and to reduce human suffering must be considered. Consideration must be given to the potential of increased capacity requirements to maintain physical activity, which will have a clear connection to health and cardiovascular disease. Therefore more study is needed to find out if NMT related AEs and recovery have effect on PA. Through research, effects of diminishing post-treatment pain should study more.

In the light of this knowledge we should take into account to encourage the use of manual therapies and NMT already in earlier states to prevent chronicity and continuous use of drugs. Long term effects of manual therapy including physical activity and therapeutically

supervising seems to be beneficial and in terms of current knowledge contains less disadvantages than continuous use of analgesics.

Conclusion

In short term AEs after Naprapathic Manual Therapy are not a prognostic factor. At long term (three months after treatment) AEs might be beneficial for men but not for women.

Practical use. Treatment related AEs should be considered as biomechanical adaptations where nociceptors are stimulated through the unloading of painful tissues. Even if patient have had AEs that does not reflect the chance to recover at short term and neither treatment should be evaluated so. Emphasis shall focus on recognizing unwanted severe changes. For the therapist point of view, knowing the AEs affection to recovery can be used as a motivating factor for therapist and patient to complete therapy sessions as well as to reassure other health care professionals to let patient complete the recovery process.

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