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Original article

Sympathetic nervous system effects in the hands following a grade III postero-anterior rotatory mobilisation technique applied to T4: A randomised, placebo-controlled trial

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ABSTRACT

Joint mobilisation to the T4 vertebra has been advocated as a treatment for T4 syndrome. To date no controlled studies have investigated the effects of thoracic spinal manual therapy (SMT) applied to T4 on sympathetic activity in the hands. This study investigated whether a grade III postero-anterior rotatory joint mobilisation technique applied to the T4 vertebra at a frequency of 0.5 Hz had demonstrably greater effects than a validated placebo intervention on skin conductance (SC) in the hands of healthy subjects.

A power analysis calculation was performed and using a double blind, placebo-controlled, independent groups design, 36 healthy subjects (18–35 years) were randomly assigned to two groups (placebo intervention or treatment intervention). A BioPac unit recorded continuous SC measures before, during and after each experimental intervention. An exit questionnaire was used to validate the expectancy effects of the placebo intervention. Results demonstrated a significant difference between groups in SC in the right hand during the post-treatment rest period ($F = 4.888$, $p = 0.034$); with the treatment intervention being sympathoexcitatory in nature. A trend towards a significant difference between groups was also demonstrated in the left hand during the rest period ($F = 4.072$, $p = 0.052$).

This study provides preliminary evidence that joint mobilisation applied to the T4 vertebra at a frequency of 0.5 Hz can produce sympathoexcitatory effects in the hand. Further research is recommended in a patient population.

1. Introduction

T4 syndrome has existed as a clinical concept for several decades and has been identified as a source of hand symptoms (Evans, 1997; Conroy and Schneiders, 2005; Mellick and Mellick, 2006). Maitland (1986) describes T4 syndrome as "*a clinical pattern that involves upper extremity parasthesia and pain with or without symptoms into the neck and/or head*". Conroy and Schneiders (2005) state that T4 syndrome "*typically presents with unilateral or bilateral glove distribution of parasthesia into the hands*". The role of joint mobilisation applied to the T4 vertebra has been advocated as a treatment for T4 syndrome (Maitland, 1986; Grieve, 1991; DeFranca and Levine, 1995; Conroy and Schneiders, 2005), however the effects of spinal manual therapy (SMT) for the treatment of T4 syndrome have not been established at a higher level of scientific evidence than case study reports.

The pathophysiology of T4 syndrome has not been established, indeed, there exists considerable academic and clinical debate regarding the ability of the joints of the thoracic region to refer pain or parasthesia to the hands (Grieve, 1988). In addition, the dermatomal distribution of the peripheral nerve supply is not consistent with the "glove distribution" of symptoms in the hand (Fuller, 1999). The sympathetic nervous system (SNS) has been suggested as a possible mechanism linking the thoracic spine to the T4 syndrome referral pattern (Grieve, 1994; Evans, 1997; Bogduk, 2002). The upper limb supply of the SNS is from T1–T9 (Bogduk, 2002), with the presence of a sympathetic vasoconstrictor network (Evans, 1997). The T4 vertebra therefore has an SNS link with the upper limb (see Fig. 1).

No controlled studies have been conducted to evaluate the effects of thoracic SMT applied to T4 on sympathetic activity in the hands. Mellick and Mellick (2006) reported relief of bilateral arm pain, glove distribution numbness, and parasthesia following intramuscular injections of bupivicaine–methylprednisolone at T4 paraspinal level in two patients with T4 syndrome. However single diagnostic blocks have been shown to have a false positive rate of

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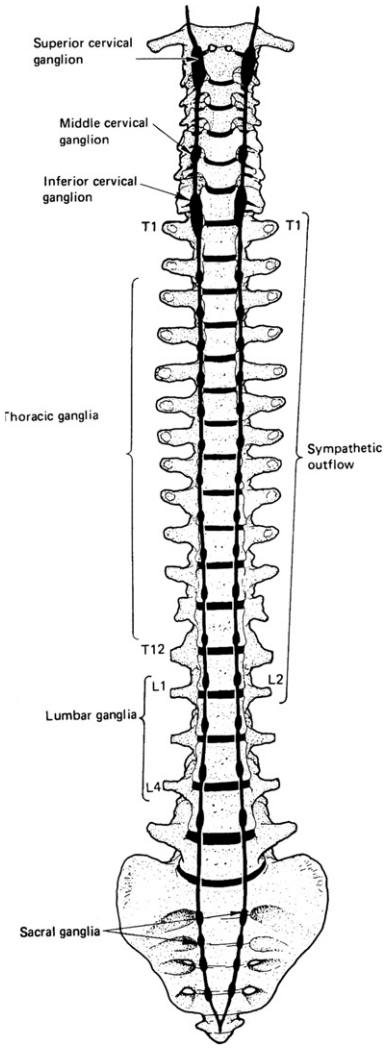

Fig. 1. The sympathetic ganglia of the spine. Reproduced with kind permission from Palastanga et al. (1990) from *Anatomy and Human Movement: Structure and Function.* Oxford: Butterworth Heinemann, Fig. 7.58, p 875.

38% in the lumbar spine facet joints (Schwarzer et al., 1994). Without control subjects or the use of double-block injections to evaluate placebo effects findings may be falsely attributed to the active drug agents and location of injection.

Initial explanations for therapeutic effects of SMT focused on mechanical effects on local soft tissue and joint structures (Evans, 2002; Potter et al., 2005). Pickar (2002) and Zusman (2004) reviewed the literature and concluded that the mechanical effects were unlikely to explain the hypoalgesic effects of SMT and supported a theoretical framework of neurophysiological effects. SMT is considered to have a neurophysiological mechanism of action through stimulation of the dorsal peri-aqueductal grey (dPAG) matter in the midbrain and is effective in producing hypoalgesic effects mediated by the pathways of the SNS (Wright, 1995; Pickar, 2002; Zusman, 2004).

The peri-aqueductal grey (PAG) consists of two discrete functional regions with specific effects: the sympathoexcitatory dPAG and the sympathoinhibitory ventrolateral PAG (vPAG). The dPAG descending pathways excite SNS activity and produce non-opiod analgesia by specifically suppressing mechanical nociceptive stimuli (Kuraishi et al., 1983, 1991; Wright, 1995). If SMT is theorised to stimulate the dPAG then hypoalgesia induced by mobilisation should correlate with an associated SNS response. Fig. 2 illustrates the specific effects mediated by the dPAG.

There have been few studies investigating peripheral SNS changes following SMT to the thoracic spine. SNS effects in the upper limbs have been reported with mobilisation to the T6 costovertebral joint in the sympathetic slump position in healthy subjects (Slater et al., 1994) and frozen shoulder subjects (Slater and Wright, 1995), however poor control of independent variables means that joint mobilisation cannot be differentiated from slump positioning as the active component in these studies.

The evidence base for cervical SMT provides further insight into SNS changes in the hand. The sympathetic chain includes ganglia at C2, C5/6 and C7 (Williams et al., 1995) and these are potentially mechanically stimulated by SMT, as well as via dPAG-mediated descending pain inhibition (Wright, 1995; Zusman, 2004).

Grade III central postero-anterior mobilisation to C5 has been shown to increase skin conductance (SC) more than placebo or control in the upper limbs of 16 pain free males (Petersen et al., 1993). Grade III C5/6 lateral glide mobilisations have been shown to increase SC greater than placebo or control in 24 pain free subjects (Vicenzino et al., 1995), and in 24 lateral epicondyalgia subjects along with hypoalgesia (Vicenzino et al., 1998). Similarly, a grade III C5 unilateral postero-anterior mobilisation has been shown to increase SC bilaterally in the upper limbs of 30 subjects with C5/6 segmental pain of more than three months duration (Sterling et al., 2001). This effect, greater than placebo, was associated with decreased pressure pain thresholds, consistent with dPAG-mediated effects (Kuraishi et al., 1983, 1991).

Chiu and Wright (1996) demonstrated sympathoexcitatory SC changes in the upper limbs at both 2 Hz and 0.5 Hz frequencies using a grade III central postero-anterior mobilisation technique to C5 in 16 pain free males. In the lumbar spine, Perry and Green (2008), in a double blind, placebo-controlled, independent groups study using 45 healthy subjects, reported a unilateral side-specific increase in SC in the left leg with the application of a postero-anterior mobilisation to the left L4/5 zygopophyseal joint at 2 Hz.

SC has therefore been shown by a range of studies to be a viable measure of SNS activity in the hand and is appropriate to the clinical presentation of T4 syndrome. All of the upper limb studies have used repeated measures designs. This is a methodological concern as it is not known how long it takes for sympathetic effects to return to baseline. Independent group designs would be better utilised to eliminate possible order effects.

This study begins to address the research-practise gap in the effects of thoracic SMT on upper limb SNS activity, and therefore a possible treatment effect in T4 syndrome. It is the first randomised controlled trial to investigate a link between T4 and sympathetic outflow changes to the hand. The study aimed to establish whether a mobilisation technique applied to the T4 vertebra had any demonstrably greater effects on the sympathetic activity in the hands than a validated placebo intervention in

dPAG stimulation effects

- Descending non-opiod analgesia
- Sympathoexcitation via nor-adrenaline mediated pathways
- Skin conductance increases
- Skin temperature decreases
- Decreased mechanical nociceptive stimuli (increased pressure pain thresholds)
- Facilitates movement (increased motor control)

Fig. 2. Specific effects of the dPAG of the midbrain.

healthy subjects. The null hypothesis stated that there would be no difference in SC measures in the hands of healthy subjects following a postero-anterior rotatory mobilisation technique applied to T4.

2. Methodology

2.1. Subjects

A convenience sample consisting of 36 healthy subjects was used (13 male, 23 female; range 18–35 years, mean 22.7 years, SD 5.2). Inclusion criteria were healthy individuals aged 18–35 years, naïve to SMT, and asymptomatic of thoracic spine, neck and upper limb pain. Exclusion criteria were used to control for factors known to influence the SNS (Benhamou et al., 1993; Slater and Wright, 1995; Chiu and Wright, 1996; Evans, 1997; Andreassi, 2000). Table 1 shows the subjects' anthropometric characteristics.

Based on Sterling et al's. (2001) intra-subject standard deviation of 16.2% (treatment group) for SC measures, a power analysis calculation revealed that 36 subjects (18 per group) would enable a difference in SC values from baseline of 16% to be detected at the 5% significance level with 80% power. A 16% SC value was selected because it was consistent with Sterling et al's. (2001) study which found a significant change in SC in the hand following SMT and it was felt by the authors to represent a clinically significant change.

Ethical approval for the study was obtained from Coventry University Ethics Committee.

2.2. Research design

A double blind, randomised, placebo-controlled, independent group experimental study design was used. Subjects were blind to which intervention they received, an important objective in placebo-controlled studies (Vincent and Lewith, 1995); and an independent assessor gathered the data. Subjects were randomly allocated to either the treatment intervention (group I) or placebo intervention (group II). An independent group design was used to eliminate order effects. Repeated stimulation of the SNS may facilitate an increased response to subsequent stimulation as physiological responses in the nervous system adapt to repeated mechanical stimulation (Lord, 1995).

2.3. Treatment intervention

A grade III rotatory postero-anterior intervertebral mobilisation consists of an oscillatory movement in three directions: postero-anterior, cephalad–caudad, and lateral. The technique involves placing two hands adjacent to either side of a single thoracic vertebral segment (T4), using a pisiform grip, and is thought to produce localised segmental joint glide at the costovertebral, costotransverse, intervertebral and facet joints of the thoracic spine (Maitland, 1986; Williams et al., 1995; Maitland et al., 2005).

The researcher stood by the right shoulder of the prone subject, placed his left hand on the right transverse process of T4 with his fingers pointing cephalad and laterally, and his right hand on the left transverse process of T4 with his fingers pointing laterally (see Fig. 3). During the technique the researcher's left hand moves postero-anteriorly, cephalad and slightly laterally; and the researcher's right hand moves concurrently postero-anteriorly, caudad and slightly laterally, to the limit of available joint range.

The treatment intervention was performed at a frequency of 0.5 Hz (30 oscillations per minute) for three sets of 1 min, with 1 min rest between sets. This has been shown to be an effective frequency for influencing SC in the hand (Chiu and Wright, 1996).

2.3.1. Pilot study to establish intra-rater reliability

To establish the consistency of the researcher (an advanced physiotherapist, 12 years post-qualification) at performing the technique, one subject was used to perform the treatment intervention technique on T4 at 0.5 Hz frequency. An Intraclass Correlation Coeffficient (ICC) value of 0.61 was calculated. An ICC of 0.6 or above is acceptable for research purposes (Chinn, 1991).

2.4. Placebo intervention

The placebo intervention was designed to closely mimic the treatment intervention. The postero-anterior rotatory pressure was applied to T4 to the limit of available range consistent with the treatment intervention technique, however no oscillation was performed. The pressure was maintained statically for 1 min, and repeated for three sets with 1 min intervals.

2.5. Research method

The experiment was performed in a temperature controlled laboratory (Janig and Habler, 2003). Subjects lay prone, arms by their side, with their cervical spine in neutral. The index and middle fingers on each subject's hands were cleaned with alcohol wipes. SC electrodes were attached to the index and middle fingers on each

Table 1
Range, mean & standard deviations for sample age, height & weight.

	Whole sample $n = 36$	Placebo of intervention group of $n = 18$	Treatment intervention group $n = 18$	Levene's test homogeneity variance (p value)
Age (years)				
Range	18–35	18–33	18–35	0.090[a]
Mean	22.72	22.00	23.44	
SD	5.26	4.29	6.11	
Height (cm)				
Range	157–187	160–180	157–187	0.034
Mean	169.58	169.61	169.55	
SD	8.28	6.38	10.03	
Weight (kg)				
Range	51–90	54–83	51–90	0.039
Mean	64.88	65.61	64.16	
SD	9.47	7.02	11.59	

[a] Non-significant value where levels of significance were set at $p < 0.05$.

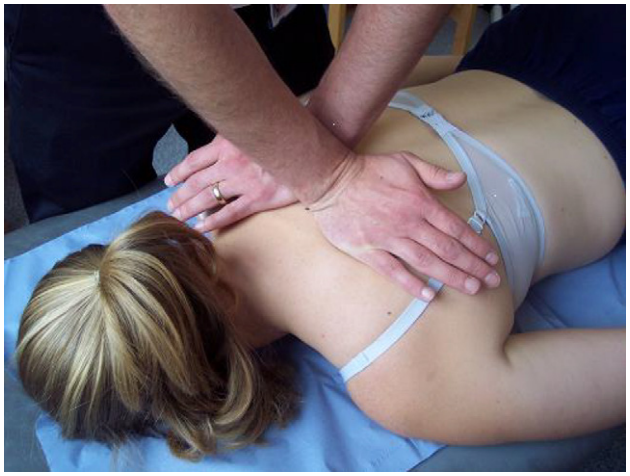

Fig. 3. Hand position for the application of the treatment technique. (Force is applied in a postero-anterior, rotatory and lateral direction).

hand using a pea-sized amount of Sigma electrode gel (0.050 molar NaCl electrolyte unibase medium). These locations are consistent with the methodology used in the study by Sterling et al. (2001). The spinous process of T4 was marked with an indelible ink pen. Intra-rater reliability of palpation of T4 in prone has been shown to be *substantial* (Landis and Koch, 1977); (0.71 expanded kappa; 95% CI 0.22–1.00 mm (Christensen et al., 2002)).

Subjects underwent an 8-min *stabilisation period to establish a physiological resting state*; followed by a 2-min *baseline period;* a 5-min *intervention* period; and a 5-min *post-intervention* period; consistent with various authors (Petersen et al., 1993; Vicenzino et al., 1995; Chiu and Wright, 1996; Sterling et al., 2001; Moulson and Watson, 2006; Perry and Green, 2008).

2.6. Exit questionnaire

To enhance internal validity a previously validated exit questionnaire was used to evaluate whether expectancy effects were greater in the treatment intervention group than the placebo intervention group (Vincent and Lewith, 1995).

2.7. Instrumentation & measurement

The BioPac system and MP30 Acquisition Box was used with SS3LA EDA finger transducers. The BioPac system has been used in 209 published studies to date, and is considered to be reliable and valid (Moulson and Watson, 2006; Perry and Green, 2008). The "Integral Measurement" was selected for use for data analysis. The integral measure is a summation of the total value of a physiological variable over a period of time, and has been used for investigating SMT and SNS activity (Perry and Green, 2008). Data was evaluated in terms of percentage change (PC) from baseline values for SC, normalised to the time period. PC from baseline was calculated using the following equation (Rowald and Tozer, 1989):

$$\%\ \text{change from baseline} = \frac{1\ \text{min measure} - \text{baseline}}{\text{baseline}} \times 100$$

3. Data analysis

The assumptions for parametric tests were met and one-way analysis of variance (ANOVA) was selected to analyse the data in order to reduce the likelihood of a Type I error (Bewick et al., 2004). Questionnaire analysis was via a two-tailed Mann–Whitney *U* test after checks that assumptions were met.

4. Results

4.1. Laboratory conditions

Room temperature was recorded at the beginning and end of each subject's experimental session (Uematsu et al., 1988). Relative constancy was demonstrated within each session (mean 24.7 °C, SD 0.29, range 24.2–25.6 °C) with maximum within subject room temperature variation of no more than 0.4 °C (mean 0.2 °C, SD 0.1, range 0.0–0.4 °C).

4.2. Homogeneity of the independent groups

Homogeneity of variance between groups was established via Levene's statistic ($p < 0.05$) for each data set and showed no significant differences (left hand intervention period 0.076; right hand intervention period 0.785; left hand post-intervention period 0.592; right hand post-intervention period 0.605).

4.3. SC differences

Table 2 and Fig. 4 display the PC from baseline values for SC in both groups. Outliers were noted but there was no clear justification for excluding them from the data analysis. During the intervention period, one-way ANOVA demonstrated that there were no significant differences in SC between the placebo and treatment interventions in the left hand ($F = 1.390$, df $= 35$, $p = 0.247$) or the right hand ($F = 1.093$, df $= 35$, $p = 0.303$). In the post-intervention period, there was a statistically significant difference in SC PC from baseline values in the right hand following a grade III postero-anterior rotatory mobilisation applied to T4 at 0.5 Hz compared to the placebo intervention ($F = 4.888$, df $= 35$, $p = 0.034$). In statistical terms this response was side-specific in the right hand but there was a trend towards a bilateral effect including the left hand ($F = 4.072$, df $= 35$, $p = 0.052$).

4.4. Subject naivety exit questionnaire

Statistical analysis of differences in responses between groups was performed for each question. The questionnaire responses showed that the credibility of the placebo intervention was at least as good as the credibility of the treatment intervention; question one ($p = 0.157$), question two ($p = 0.707$), and question three ($p = 0.793$). A significant difference was found in response to question 4 ($p = 0.049$) where expectancy effects were greater in the placebo intervention group. Overall, the placebo intervention was considered as appropriate for investigating of the specific effects of the treatment intervention technique separate from expectancy effects.

5. Discussion

There is evidence to reject the null hypothesis and support the alternative that there is a significant difference in SC in the hands following the treatment intervention compared to the placebo intervention; and this response is side-specific (right hand rest period, $F = 4.888$, df $= 35$, $p = 0.034$).

Table 2
PC from baseline measures and One-way ANOVA for SC.

	Placebo intervention $n = 18$				Treatment intervention $n = 18$				One-way ANOVA				
	During treatment		Post-treatment		During treatment		Post-treatment			During treatment		Post-treatment	
	Left	Right	Left	Right	Left	Right	Left	Right		Left	Right	Left	Right
Mean	0.21	2.38	−9.20	−12.38	5.16	8.12	1.56	4.47*	**Df**	35	35	35	35
SD	9.71	17.03	13.66	18.73	14.94	15.91	18.05	26.18	***F* value**	1.390	1.093	4.072	4.888
95% CI	−4.62 to 5.04	−6.08 to 10.85	−15.99 to −2.40	−21.62 to −2.98	−2.26 to 12.95	0.21 to 10.54	−7.40 to 10.54	−8.54 to 17.49	***p* Value**	0.247	0.303	0.052	0.034*

*Statistically significant value where the level of significance is set at $p < 0.05$.

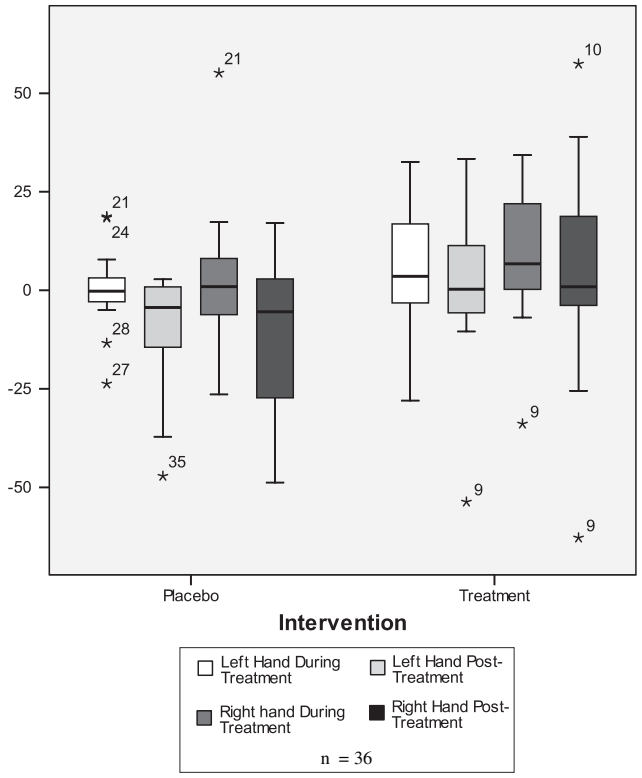

Fig. 4. Cluster boxplot (including error bar) illustrating the distribution of SC measures during the experimental period for the both hands (* represents extreme subject values and subject number).

The findings of the study demonstrated that the treatment intervention was sympathoexcitatory in nature, with mean PC from baseline (PC) values for SC ranging from 1.56% (SD 18.05) to 8.12% (SD 15.91). Statistically, a unilateral effect was shown in the post-intervention period (right hand $F = 4.888$, df $= 35$, $p = 0.034$), with a trend towards a statistically significant bilateral effect (left hand $F = 4.072$, df $= 35$, $p = 0.052$).

The present study shows that changes in SNS measures in the hands can be measured following SMT to the thoracic spine. In the right hand, the mean PC for SC measures were 5.74% greater in the treatment group than placebo during the intervention period, and 16.85% greater than placebo during the post-intervention period. In the left hand, the mean PC for SC measures were 4.95% greater in the treatment group than placebo during the intervention period, and 10.56% greater than placebo during the post-intervention period. Comparison of the mean PC values with previous studies is not appropriate as previous upper limb studies were repeated measures designs. The authors acknowledge that it may be possible that a sustained pressure placebo technique may affect SNS activation and this is one of the methodological issues in selecting a credible placebo that mimics the treatment intervention.

The side-specific effects appear to be due to the oscillatory nature of the technique. The common feature of all the joint mobilisation techniques demonstrating upper limb SNS effects is joint oscillation (Petersen et al., 1993; Slater et al., 1994; Vicenzino et al., 1994; Slater and Wright, 1995; Vicenzino et al., 1995; Chiu and Wright, 1996; Vicenzino et al., 1998, Sterling et al., 2001). Stimulation of the dPAG of the midbrain is central to the evidence base for SMT and the sympathoexcitatory findings of the present study are further evidence for this mechanism. Joint oscillation may also stimulate spinal reflex pathways (Dishman and Bulbulian, 2000; Dishman et al., 2002a,b; Dishman and Burke, 2003); the sympathetic ganglia anterior to the rib heads; or a combination of these. Biomechanical explanations of joint opening/closing are incongruent with the near significant findings ($F = 4.072$, df $= 35$, $p = 0.052$) in the contralateral hand. This study sought to control possible experimental variants such as joint opening and closing by standardising the side the researcher was positioned and the direction the technique was performed. Future studies could investigate possible differences in effect in relation to the direction of mobilisation.

Several authors have reported bilateral sympathoexcitatory effects as evidence of a dPAG-mediated response to SMT (Slater et al., 1994; Vicenzino et al., 1994; Slater and Wright, 1995; Sterling et al., 2001). The present study found unilateral effects ($F = 4.888$, df $= 35$, $p = 0.034$) with a trend towards a significant bilateral effect of smaller magnitude ($F = 4.072$, df $= 35$, $p = 0.052$). On closer scrutiny of previous thoracic spine studies it can be seen that reported bilateral responses are often of different magnitude from one side to the other (Slater et al., 1994). Specific mediation within global dPAG effects is a possible mechanism. Fuller understanding of the mediation of the midbrain by the brainstem and medulla may assist in achieving a fuller understanding of the variations in sympathetic effects seen in SMT studies.

The results of this study support the findings of other studies that demonstrate that SMT applied to the cervical spine (Petersen et al., 1993; Vicenzino et al., 1994, 1995; Chiu and Wright, 1996; Vicenzino et al., 1998; Sterling et al., 2001; Moulson and Watson, 2006), and the thoracic spine (Slater et al., 1994; Slater and Wright, 1995), have a sympathoexcitatory effect in the upper limbs. Perry and Green (2008) have also shown that SMT applied to the lumbar spine has a side-specific sympathoexcitatory effect in the lower limbs.

An SNS pain mechanism commonly presents with sudomotor changes (cold peripheries and increased sweating) and vasomotor changes (blanching of the skin) (Siddall and Cousins, 1997). Upper extremity coldness has been reported in T4 syndrome (Mellick and Mellick, 2006) and this is consistent with a sympathoexcitatory pain mechanism. SMT is an appropriate treatment choice to aim to improve higher centre-mediated modulation of pain. Another possible mechanism involved in clinical efficacy is the "rebound phenomenon", where following stimulation sympathetic measures return to levels below their pre-stimulus values (Andreassi, 2000). In T4 syndrome this may move the baseline SNS activity closer to normal levels.

This study is the first to investigate a thoracic spine mobilisation technique applied in isolation and demonstrate a sympathoexcitatory effect. It is the first randomised controlled trial to investigate and establish a link between T4 and sympathetic activity in the hand, supporting a theoretical link between the SNS and T4 syndrome, albeit in subjects without symptomology. The findings give support to the theoretical framework for the selection of SMT to T4 to influence the sympathetic outflow to the hands and potentially the hand symptoms seen in T4 syndrome, however care should be taken in extrapolating the study findings to a patient population. Further research into sympathetic effects in T4 syndrome in a patient population is recommended.

6. Conclusion

A grade III postero-anterior rotatory mobilisation technique applied to the T4 vertebrae at a frequency of 0.5 Hz produced a side-specific sympathoexcitatory increase in SC in the hand, which statistically is significantly greater than a validated placebo mobilisation technique. Furthermore, there is a trend towards a statistically significant bilateral sympathoexcitatory effect which may be of clinical relevance.

The effective component of the technique appears to be the oscillatory component. The findings suggest that a dPAG-mediated sympathoexcitatory response occurred as reported in other studies, and may also support the theory of a possible local mechanism such as stimulation of the sympathetic ganglia or spinal segmental pathway.

There is a need for further research to expand the knowledge base of thoracic SMT in T4 syndrome into randomised controlled trials in a patient population, and to establish if there is any correlation between SNS effects and hypoalgesia.

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