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Original Article

Immediate effect of T2, T5, T11 thoracic spine manipulation of asymptomatic patient on autonomic nervous system response: Single-blind, parallel-arm controlled-group experiment

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A B S T R A C T

Purpose: Investigating the immediate effect of thoracic spinal manipulation on autonomic nervous system targeting three segments arbitrarily chosen, T2/T5/T11, compared to a sham-treatment randomised controlled group.

Methods: 73 participants completed the study protocol. *Paired-t test* were used to compare within-group and *ANOVA repeated measures* for between-groups results. Subjects were randomised into a single-blind controlled trial involving two study groups: intervention group and sham treatment group. Outcome measure was the rMSSD, electronically recorded through R-R intervals, continuously registered over a period of 60 s before and 60 s after the manipulation/sham.

Results: Within-group and between-group changes suggest a significant increase in rMSSD ($p < 0.05$) in intervention group compared to sham treatment, immediately after the postero-anterior thoracic HVLAT.

Conclusion: The result of this study suggests that thoracic OMT could affect ANS balance with a shift towards parasympathetic increase activity. Due to population sample, this study shouldn't be used for clinical application, but as a baseline for future research on the argument.

Introduction

Homeostasis can be defined as the result of the stability of physiological systems that maintain life maintained within a narrow range for the current life history stage [1]. The homeostatic balance is considered as a change of state compatible with the actual environmental situations [2]. *Allostasis* is the reaching of physiological stability through a change of homeostatic state [1,3].

Allostatic and homeostatic control are ruled by the autonomic nervous system (ANS) integrated within the central nervous system (CNS) [2]. A disorder of the ANS can affect the homeostatic and allostatic processes, altering the allostatic adaptations: temporary processes during environmental changes. If not turned off when not needed, if they occur too frequently or fail to occur at all, it could facilitate the development of systemic diseases such as hypertension [4], baroreflex failure for blood pressure regulation [5], type II diabetes or affect the immune system and the inflammatory process [6]. Moreover, it has been demonstrated how the ANS is strictly correlated to the modulation of pain perceived by the subject [35].

The osteopathic profession has long been recognised as a relationship between the autonomic nervous system and the function of the body in health and disease [7]. Despite the increasing interest in this area, little is known about the influence of High Velocity Low Amplitude Thrust (HVLAT) on the Autonomic Nervous System (ANS).

Bialosky et al. [34] proposed a reference model for the interaction between Manual Therapy techniques and ANS, highlighting two different responses: spinal cord and supraspinal mediated effect as hypoalgesia, autonomic response (Skin temperature, skin conduction, cortisol levels, heart rate), and mechanical outcomes. Despite that, the model is primarily based on associated response instead of direct observation of region of interest, allowing a more critical and precise outcome measure; moreover the HVLAT has not been examined for this model.

On the other hand, a comprehensive review of Ref. [36] on the effect of Spinal Manual Therapy and experimental induced pain, showed a local/regional hypoalgesic effect for some types of stimuli (more effective on pressure pain than temperature pain).

Sillevis et al. [8] examined in an RCT study, the influence of T3-T4 thrust on patients with chronic pain; collecting data about pain perception and pupil dilation, in order to evaluate the autonomic response. The results obtained in 101 patients showed that manipulation did not result in a change in sympathetic activity nor pain perception

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(p = 0.961).

Root mean square of successive difference (rMSSD) through Heart Rate Value is the outcome measured. HRV is a *"non-invasive electrocardiographic marker reflecting the activity of sympathetic and vagal component of the ANS on sinus node of the heart"* [33]. It expresses the total amount of variations in the intervals between QRS complex [9,10].

The lack of evidence about the neurological induced response of HVLAT in the ANS has been the main rationale behind conducting this research. The examination of asymptomatic participants allowed us to create a sample of data that can be used for future study, thus examining more precisely the ANS modulation obtained with HVLAT technique.

The original hypothesis was that thoracic HVLAT was able to increase parasympathetic activity in asymptomatic participants.

Methods

Design

Single blind, placebo controlled, simple randomised (1:1) parallel-group pilot study conducted in London, England (2 sites); testing one dependant variables, Mean Square of the Successive Differences rMSSD, as primary outcome following postero-anterior thoracic thrust technique. Report to Fig. 1 for the experimental design process.

Variables

Independent variables

- Postero-Anterior Thoracic High-Velocity Low Amplitude Thrust Technique
- Sham Technique

Dependant variables

- rMSSD for evaluation of parasympathetic modulation

Subjects

Asymptomatic subjects between 18 and 45 years of age were recruited. The age was determined by considering the change in response and activity of ANS related with ageing [11]. Posters around the UCO were the main form of recruitment. Additionally, an email was distributed using FirstClass Mass Mailer [37] containing the Participant Information Sheet (PIS) next to a short introduction and list of exclusion and inclusion criteria (Table 1). All available participants were screened for eligibility using Health Screening Questionnaire and a physical examination performed by the researcher. Any ticks in the YES boxes of the questionnaire precluded them from participating. Patients were instructed not to take any medication that could alter the functioning of the autonomic nervous system for at least 24 h before participating in the study. All patients were instructed not to consume caffeinated drinks, smoke, or eat anything for at least 12 h before the study. A meeting were scheduled in order to assess physical examination to ensure absence of exclusion criteria, assign the alphanumeric code and organise the participant timetable for the experiment. It was clearly stated that participation was completely voluntary and that withdrawing at any time will have no consequences. The recruitment period start in late January 2016 until March 2016. Data were recorded over a period of three different days in the same week for each participant. All the data were collected over a period of one month (April 2016).

Outcome measure

RMSSD was used as main outcome, measured with Polar H7 Heart Sensors© chest band. It expresses the total amount of variations in the intervals between QRS complex [9,10]. Due to the ambiguity in physiological meaning in LF variations during short recording periods [12] the analysis was restricted to Time Domain Indices (rMSSD), more reliable than frequency domain [13], and considered as PNS modulation indices [12]. R-R intervals is a time domain measure of HRV calculated by the equation of Kim et al. [14]. According to Hayward et al. [15]; the rMSSD time domain measurement has high sensitivity to identify ANS modification in temporal window of 1–2 min; and has been previously

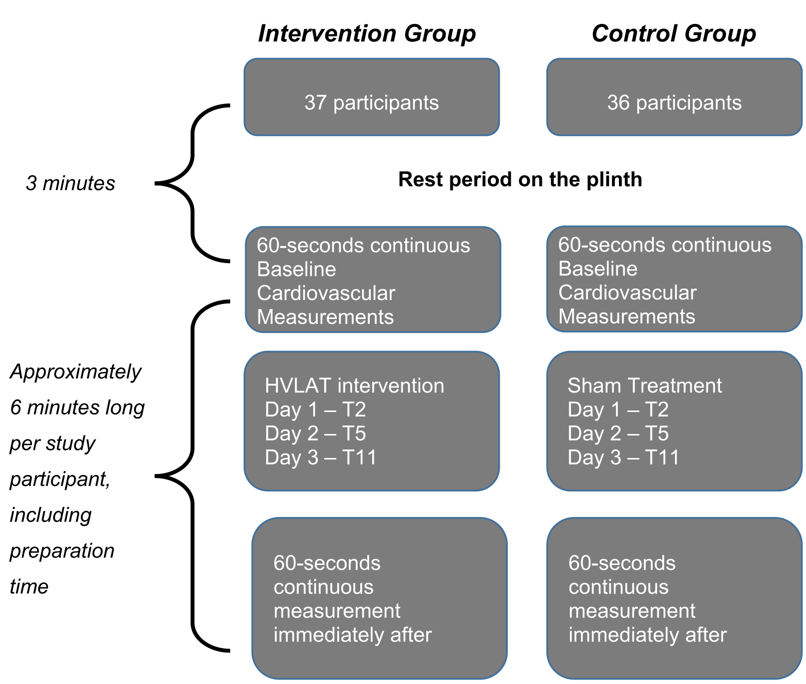

Fig. 1. Experimental design process.

Table 1
Exclusion and inclusion critera.

Exclusion Criteria	Inclusion Criteria
• ANS disease (i.e. Horn's Syndrome) • Chronic condition affecting ANS (i.e. Diabetes) • Thoracic Disease (i.e. thoracic malformation) • Presence of fracture in the thorax happened less than 1 year ago • Chronic Respiratory Disease (i.e. severe Asthma or COPD) • Neoplastic Pathologies • Chronic Low Back Pain • Used two or more alcoholic beverages daily • Diagnosed Rheumatologic Condition • Diagnosed Osteoporosis • Diagnosed Atherosclerosis • Heart pathologies • Use of drugs as beta-blockers or warfarin, affecting the heart.	• Age comprised between 18 and 45 years • Adequate understanding of English language • Ability to give informed consent • Ability to lay down in supine position for 10 min

used for ANS assessment [8,16].

Study protocol

The experimental study took place on the second floor of the UCO and at UCO Clinic (London), silent and quiet rooms were used in a professional clinical environment 73 participant were assigned randomly to the Intervention OR Control group. The concealed random association was made with Excel prior to the beginning of the study. Three different segments were arbitrarily chosen for this study: T2, T5 and T11; as aforementioned the research addressing ANS and HVLAT has been made primarily on the cervical spine or at T4 level; thus we identified 3 segments not examined yet. The thoracic spine has been chosen due to presence of the sympathetic chain location. Both manipulation and sham treatment had been performed by the same practitioner: a fully qualified General Osteopathic Council (GOsC) registered and technique teacher of the University College of Osteopathy in London (UCO), UK.

Procedures

Each participants received High Velocity Low Amplitude (HVLAT) manipulation OR Sham intervention at every segment on three different days. During the measurement phase, all patients lay supine with a pillow under the neck in a quiet room for 3 min before the test, in this way there was a relaxing and lowering of possible stress influence on the SNS [17]. After 3 min of accommodation, the HRV was measured continuously for a 60-s duration. Directly after the baseline measurement, the participant received either manipulation or sham intervention (Fig. 1). The manipulation consisted of high-velocity, mid-range, postero-anterior force to the thoracic spine targeting T2-T3/T5-T6/T11-T12 segments. Before the manipulation application, the right thenar eminence of the practitioner was placed on the marked transverse process of the chosen segment. In order to create capsular tension at the segment before the manipulation, added components of segmental flexion, rotation, side bending, and some slight compression of the participant's chest were introduced using the researcher's own chest and left arm. The right hand simultaneously performed a pronation of the right forearm and a slight distraction toward the pelvis, thereby further tightening the capsule. When the tissue barrier was felt, the manipulation manoeuvre will be achieved by pushing the participant's elbows toward the shoulders [18]. No second attempt was made if no audible pop was achieved. The sham treatment consisted of an open-hand placement in a way that it should not result in a manipulation at the segment previously chosen, as described by Cleland et al., [19]. The practitioner's hand was placed flat under the chosen segment. The participant crossed the arms over the chest, and in this position with minimal mobilization and without manipulation effect, the practitioner instructed the participant to inhale deeply followed by exhalation, at that time a light 3 s compression of the arms into the chest was performed. Immediately after the intervention HRV measurement were continuously taken for 60 s.

Randomisation and concealing

Concealed allocation was performed by using an Excel computer-generated randomised table of alphanumeric-code (ID) created before the beginning of the study. Following the simple randomisation procedure, the ID was assigned to one of the two groups (1:1). The ID code was used throughout the study in substitution of participants' sensitive data. The ID code was reported on the participant's Health Screening Questionnaire and Consent Form and placed in sealed opaque envelopes. The main researcher and the practitioner were aware of the participant group composition.

Statistical analysis

According to Billingham et al. [20]; the sample for a pilot study with two arms is 36 participants per group, for a total of 72 participants, using the equations reported by Zhong [21]. Mean data will be reported with 95% confidence intervals to indicate precision of the estimates for the population parameters. HRV values were processed by Polar Precision Performance SW© in order to extract the R-R intervals from every measurement. Raw data were then imported into Excel (Microsoft Co., 2015) for artifacts and ectopics error inspection; rMSSD were then extrapolated using Kim's equations [14]. Data analysis was performed using statistical software package SPSS (IBM, 2015). Results were reported as mean ± standard deviation (SD) unless otherwise specified. The α level of $P \leq 0.05$ was considered statistically significant for between-group and within-group variable analysis. Levene's test was used to observe homogeneity of variance. Based on Kurtosis and Skewness tests results, the assumption for parametric descriptive statistic was satisfied for both groups pertaining to gender, pre- and post-intervention rMSSD values. Paired t-tests were performed for measuring the difference within group whilst ANOVA repeated measures for differences between groups. Effect size, as Cohen's d, was determined for the findings of each paired-samples *t*-test.

Results

Baseline results

A total of 81 potential participants were assessed for eligibility (Fig. 2), 4 of these were excluded due to presence of exclusion criteria and health screening questionnaire results. The remaining 77 were enrolled in the study; 4 participants were not able to attend all the sessions, in order to avoid incomplete data they have been excluded. Baseline results for each groups is shown in Table 2. No baseline tests has been performed, accordingly to CONSORT guidelines [22]: 73

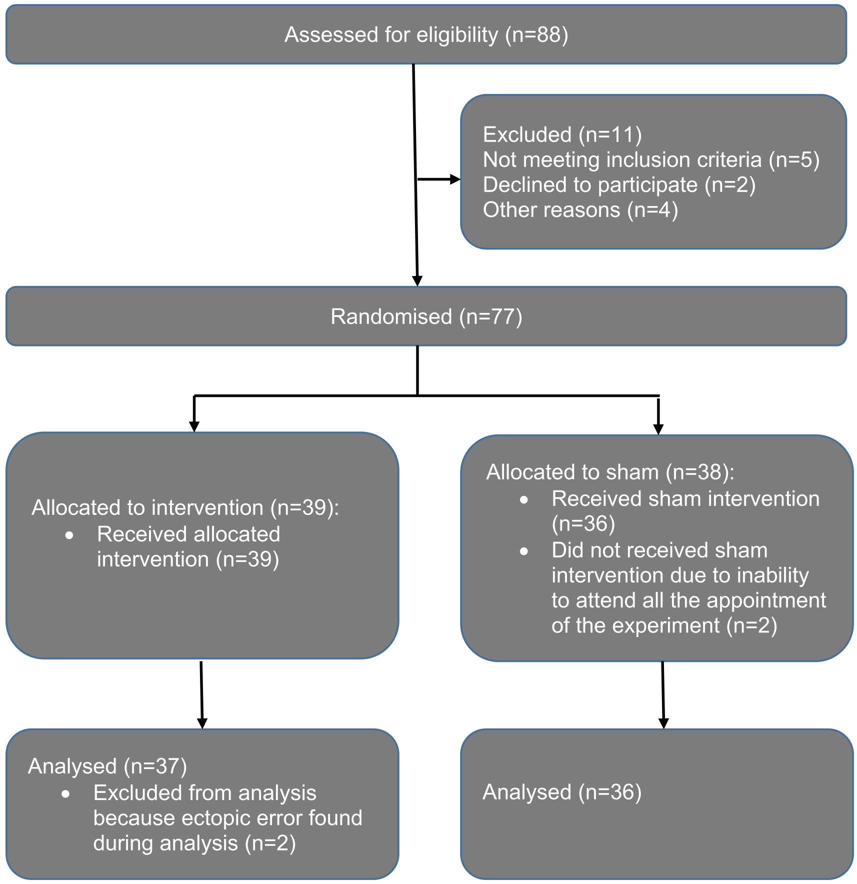

Fig. 2. Flow diagram of the progress through the phases of a parallel randomised trial of two groups.

Table 2
Baseline results.

	INTERVENTION	CONTROL
SEX (M/F)	18/19	19/17
AGE (YEARS)	25.2(± 4.3)	24.4(± 3.9)
T2 – BASELINE (MS)	25.1(± 10.2)	17.8(± 7.2)
T5 – BASELINE (MS)	18.5(± 3.4)	19.3(± 6.8)
T11 –BASELINE (MS)	29.1(± 5.3)	20.0(± 66)

Participant completed the experiment (Fig. 2).

Changes in HRV

A paired-samples *t*-test was used to determine whether there was a statistically significant mean difference between the rMSSD values pre- and post-spinal thoracic manipulation compared to a sham treatment and between per- and post-differences in the same group. No outliers were detected more than 1.5 box-lengths from the edge of the box in a boxplot. Shapiro-Wilk's test assessed assumption of normality for control (T2$p = 0.957$; T5$p = 0.217$; T11$p = 0.259$) and the intervention group (T2$p = 0.491$; T5$p = 495$), except for T11 intervention group ($p = 0.049$). Considered the minimal variation from the *null hypotheses* (p = 0.50) and the resistance of paired-t test towards minimal variation from normal distribution, the data has been implemented. There was a statistically significant within-group difference for the intervention group (T2$t(36) = 9.974$; $P < 0.05$; T5$t(36) = 8.094$, $P < 0.05$; T11t$(36) = 10.619$, $P < 0.05$), with an average mean of 21.06(± 13.58 ms). There wasn't significant difference in control group outcome (T2$t(35) = 1.804$; $P < 0.80$; T5$t(35) = 0.597$, $P < 0.554$; T11t$(35) = 0.374$, $P < 0.711$), with an average mean of 1.12(± 6.3 ms), as shown in Table 3.

Table 3
Paired-t test results within group mean rMSSD in millisecond, degree of freedom, t values, p values; for Intervention and Control group.

	Segment	Mean	*df*	*t*	*p*	*d*
Intervention Group	T2	24.34 (± 14.84)	36	9.974	p < 0.05	1.64
	T5	23.09 (± 15.77)	36	8.904	p < 0.05	1.46
	T11	14.54 (± 8.3.)	36	10.619	p < 0.05	1.75
Control Group	T2	2.398 (± 8.0)	35	1.804	p = 0.80	0.30
	T5	0.674 (± 6.2)	35	.597	p = 0.554	0.11
	T11	0.294 (± 4.7)	35	.374	p = 0.711	0.06

A repeated measures ANOVA on post-test minus pre-test parasympathetic outcome response difference scores with one within participants variable (Location, 3 locations: thoracic vertebra T2, thoracic vertebra T5, thoracic vertebra T11) and one between participants variable (Group: HVLAT, Shame) was conducted in the R statistics software [23] using the ez ANOVA package [24]. There were significant main effects of Group ($F(1,71) = 154.7$, $p < 0.001$) and Location ($F(2,142) = 7.2$, $p = 0.002$) and a significant interaction of Group and Location ($F(2,142) = 3.9$, $p = 0.029$). Mauchly's tests for sphericity were significant for the within participants tests including Location, therefore Greenhouse-Geisser epsilon corrected p values are reported. In planned comparisons of group for each location, the HVLAT group showed significantly greater parasympathetic response than the Sham group, T2, $t(55.4) = 7.9$, $p < 0.001$, T5, $t(47.1) = 8.0$, $p < 0.001$, T11, $t(57.3) = 9.0$, $p < 0.001$. Levene's tests were significant for all t tests, equal variances not assumed values given as shown in Table 4.

Table 4
ANOVA repeated measures test in millisecond.

	HVLAT		Sham	
	Mean	95% CI	Mean	95% CI
T2	24	(20–29)	0.2	(0.0–0.5)
T5	23	(18–28)	0.1	(-0.1–0.3)
T11	15	(12–17)	0.0	(-0.1–0.2)

Discussion

The results of the current study investigating the immediate effect of thoracic spinal manipulation on autonomic nervous system targeting three segments arbitrary chosen, T2/T5/T11, showed that mean rMSSD in the intervention group exhibited a significant increase in value ($p < 0.05$) within group and between groups ($p < 0.05$), whilst the control group did not show significant differences pre- and post-sham ($p > 0.05$). The mean difference was statistically significantly different from zero, therefore we can reject the null hypothesis and accept the alternative hypothesis. At date research focused mainly on the upper thoracic spine. Our results are not concordant with Sillevis et al. [8]; who showed with an RCT double-blinded on 101 patient with chronic neck pain how thoracic spinal manipulation at T3-T4 segment did not alter the sympathetic-parasympathetic balance measuring pupil diameter as outcome ($p = 0.961$); or Ward et al. [25]; who indicated with a single-blind controlled trial that anterior mobilization of the thoracic spine did not produce relevant changes in the cardiac function. Reis et al. [26]; on the other hand, performed a controlled-trial with immediate follow-up on 30 patients showing how the poster-anterior glide technique on women with fibromyalgia increased the rMSSD for a significant value ($p < 0.05$). The attempt of this study to perform a segmental-specific manipulations compared to the non-specific manipulation of Sillevis, Ward and Reis, and the evaluation of the same technique on only one outcome measures allowed for a more precise data collection.

The function of sympathetic and parasympathetic nervous system must be maintained in balance for a correct *homeostasis* [27,28]. One concern regarding this issue is that HRV studies are quite sensitive to a number of factors as eloquently pointed out by Piché & Descarreaux [29]; which can make data interpretation challenging.

Study limitations

This study informs us of the immediate effect that one type of segmental specific postero-anterior thoracic HVLAT has on the ANS in healthy, asymptomatic subjects. It is possible to enhance the validity of the study with a multi-week study or performing different types of manipulation.

One of the main issues we must accept is the limitation of external validity. The sampled population was entirely composed of osteopathy students who regularly receive spinal manipulation. Although that could reduce the startling reaction to manipulation at the impulse moment, and subsequent possible sympathetic stimulation, it is possible that the general public who don't receive regular OMT, may react differently.

Despite the fact that rMSSD could reflect immediate parasympathetic changes, it is also easily affected by external factors such as room temperature, noise, level of stress, breathing pattern and light [17]. Even though there was a resting period pre-baseline, and quiet room chosen for the experiment, it wasn't possible to create an environment that ensure a non-alteration of the ANS.

In order to increase reliability, a double-blind study should be performed. The concealment procedure should incorporate external involvement for preventing selection bias [30]. Despite the blinding process, some subjects could have been aware of the group which they belong, this may have affected the final outcome measure.

Ross et al. [31] showed that the location of the cavitation during thoracic manipulation appeared to be accurate in slightly more than 50% of the cases. The findings of Herzog et al. [32] supported his findings, demonstrating that, during a prone thoracic HVLAT, the contact area is much greater than would be necessary for one segmental level.

More variables should have been measured for a better understanding of the cardiac variation subsequent to a possible ANS alteration in activity. Blood pressure, oxygenation, and pulse should receive continuous recording.

Conclusion

This study investigated the immediate effect of thoracic spinal manipulation on autonomic nervous system, targeting three segments arbitrarily chosen, T2/T5/T11. The results showed a significant increase in rMSSD values in the intervention group (within-group and between-groups comparison). The control group did not show significant alteration in the sympathetic-parasympathetic activity after the sham intervention. The implications of this research in this field, support that segmental specific OMT appears to impact autonomic activity by enhancement of PNS in the sort-term post-manipulation. Further research should investigate long-term effects and sample a general population not aware of OMT technique type. The results from this study should be used as baseline for future study.

Ethics

Ethical approval was granted by the University College of Osteopathy's Research Ethics Committee (UCO REC).

Other information

No funding was received. No conflicts of interests were reported for this study.

Conflicts of interest

None.

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