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The Immediate Cardiovascular Response to Joint Mobilization of the Neck - A Randomized, Placebo-Controlled Trial in Pain-Free Adults

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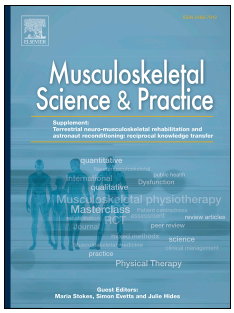

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THE IMMEDIATE CARDIOVASCULAR RESPONSE TO JOINT MOBILIZATION OF THE NECK- A RANDOMIZED, PLACEBO-CONTROLLED TRIAL IN PAIN-FREE ADULTS

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Abstract

Background: Some normotensive patients can have a spike in resting systolic blood pressure (SBP) in response to acute neck pain. Applying the typical dosage of mobilization may potentially result in a sympatho-excitatory response, further increasing resting SBP. Therefore, there is a need to explore other dosage regimens that could result in a decrease in SBP.

Objectives: To compare the blood pressure (BP) and heart rate (HR) response of pain-free, normotensive adults when receiving unilateral posterior-to-anterior mobilization (PA) applied to the neck versus its corresponding placebo (PA-P).

Study Design: Double-Blind, Randomized Clinical Trial

Methods: 44 (18 females) healthy, pain-free participants (mean age, 23.8 ± 3.04 years) were randomly allocated to 1 of 2 groups. Group 1 received a PA-P in which light touch was applied to the right 6th cervical vertebra. Group 2 received a PA to the same location. BP and HR were measured prior to, during, and after the application of PA or PA-P. A mixed-effect model of repeated measure analysis was used for statistical analysis.

Results: During-intervention, the PA group had a significant reduction in SBP, while the placebo group had an increase in SBP. The change in SBP during-intervention was significantly different between the PA and the placebo group (p-value=0.003). There were no significant between-group differences found for HR and diastolic BP (DBP). The overall group-by-time interaction was statistically significant for SBP (p-value=0.01).

Conclusions: When compared to placebo, the dosage of applied PA resulted in a small, short-lived drop in SBP not exceeding the minimal detectable change.

Trial registered at Germanctr.de (DRKS00005095).

Key words*:* cervical spine, clinical trials/intervention, joint mobilization, blood pressure, heart rate

1. INTRODUCTION

Neck pain is a common condition, ranking as the fourth most burdensome disease worldwide. Evidence suggests that rates of recurrence and chronicity are high (Borghouts et al., 1998; Hoving et al., 2001), which results in considerable functional and economic implications (Vos et al., 2012). Joint mobilization (JM) is widely acknowledged as an effective intervention (Childs et al., 2008). However, a Cochrane review indicated that the most effective cervical JM dosage has yet to be determined (Gross et al., 2010). Multiple studies have established a sympatho-excitatory effect resulting from cervical JM (McGuiness et al., 1997; Vicenzino et al., 1998; La Touche et al., 2013). On the contrary, Yung et al. (2014) developed a distinctive dose using anterior-to-posterior pressures (AP) of the cervical spine that resulted in a reduction in heart rate (HR), suggesting a sympatho-inhibitory effect. Therefore, it is indeterminate whether cervical JM results in sympatho-excitatory or sympatho-inhibitory effect if the dosage (Yung et al., 2015) is different from the traditional 3 sets of continuous 30-90 second regimen.

Maitland's (Maitland et al., 2005) central and unilateral posterior-to-anterior glides (PA) are similar entry-level forms of JM commonly used by physiotherapists worldwide. AP and PA appear more efficacious for pain relief and outcomes in patients with unilateral neck pain compared to other JM techniques such as transverse pressures and cervical rotational techniques (Egwu, 2008). Unlike central posterior-to-anterior glide and AP, PA has not been investigated for its cardiovascular profile. The neurophysiological system that alters pain overlaps with blood pressure (BP) as observed in BP-related hypoalgesia (Vicenzino et al., 1998, Sterling et al., 2001). This relationship between pain and cardiovascular function, such as BP and HR, is well explicated throughout the literature. The acute awareness of pain chiefly leads to a sympatho-excitatory effect, whereas a reduction in pain results in a sympatho-inhibitory effect (Campbell & Ditto, 2002, Wright, 1995). Numerous studies support an inverse relationship between resting BP levels and acute pain sensitivity in the normal range of BP

(Bruehl et al., 1992, McCubbin and Bruehl, 1994, Fillingim and Maixner, 1996, Myers et al., 2001). Conversely, emerging evidence suggests that chronic pain could alter this relationship; reversing it, in which the resting BP is elevated along with increased pain sensitivity and heightened clinical pain intensity (Bruehl et al., 2002, Bragdon et al., 2002). Therefore, in many chronic pain conditions (Bragdon et al, 2002, Maixner et al., 1997, Bruehl et al., 2008, Bruehl et al., 2002, Chung et al., 2008, Bruehl et al., 2010), BP-related hypoalgesia is diminished or absent. A large epidemiological study indicated that chronic low back pain is associated with a 50% increased risk for hypertension (Von Korff et al., 2005). Current evidence suggests that there is a 5.5% greater prevalence of hypertension among patients with chronic pain than among individuals not reporting chronic pain (Olsen et al., 2013). This hypertensive phenomenon becomes increasingly relevant because it has been associated as a risk factor for cervical artery dissection or CAD (Rushton et al., 2014) when compared to age-matched controls (Debette et. al. 2011). Notwithstanding, the overall incidence of CAD or vertebral artery dissection (VAD) is approximately 1-1.5 per 100,000 (Lee et al., 2006, Bogousslavsky J, et al., 1987). Heretofore, VAD has been estimated as a cause of stroke in as many as 1 in 20,000 spinal manipulations. Nevertheless, for the manual therapist, the risk may increase as a patient associated with VAD undergoes joint manipulation of the neck. (Saeed et al. 2006, Hufnagel et al., 1999). Though circumstantial, it has been the experience of the primary author, that some typically normotensive (i.e. 120/80 mmHg) adults can have a 30-mmHg or greater upsurge in resting SBP in response to acute neck pain. Therefore, if the dominant paradigm of sympatho-excitatory reaction is anticipated, clinical reasoning suggests that applying the typical JM dosage of 3 sets of 60 seconds may result in a deleterious increase SBP. Thus, it is essential to explore other dosing regimens of applying the same or similar technique to determine if a decrease in SBP is attainable, offering the benefit of pain relief without the resultant increase in SBP. Hence, BP is a pertinent and easily quantifiable variable to examine to ensure appropriate and safe application (Taylor and Kerry, 2013). Currently, there is scant evidence on the

cardiovascular response to a PA mobilization.

Consequently, the goals of this study are to assess the cardiovascular response in healthy, normotensive individuals during: (1) PA when performed in a different dosage regimen; (2) and contrast the response with its placebo equivalent.

2. METHODS

44 (18 females) pain-free subjects (mean age, 23.8 ± 3.04 years) participated in this double-blind, randomized clinical trial. Recruitment was performed whereby a mass email invitation was sent out to all staff, faculty, and students at two universities. Eligible enrollees had no prior exposure to PA of the neck, no history of syncope, no cardiovascular disease, and no cervical-shoulder pain. Participants were excluded if they were taking oral or hormonal contraceptives. The volunteers were instructed to avoid the following: ingesting caffeinated drinks within four hours of the study, drinking alcoholic beverages during the day of the study, or engaging in moderate to vigorous exercise during the day of the study as these may affect the cardiovascular dependent variables. The Ethics Committee of two universities approved the protocol of the study. All research subjects signed an informed consent form prior to participation, and their rights were protected. The study (recruitment and follow-up) was conducted between September 15, 2013 and October 14, 2015. This trial was registered at Germanctr.de (DRKS00005095).

Once the informed consent was signed, the participants were randomly allocated by two assistant investigators at each university to either one of the two groups using a computer-generated number system. This allocation was concealed in an envelope. The randomized block design was adhered to in order to equalize the number of participants in each group. The therapist and the participants did not know the random allocation number (1, experimental; 2, control/placebo), as this was concealed until within 30 seconds before the procedure. Based

on the allocation sequence, the assistant placed a card, indicating either PA-P (placebo/control group) or PA (experimental group), face down on the treatment table. Within 30 seconds before applying the intervention, the therapist turned over this card to determine which technique to perform. Throughout the entire data-collection process, both the therapist providing the intervention and the participants was blinded to the measured primary outcome variables: HR, SBP and diastolic BP (DBP).

Each participant laid prone in a relaxed position, and the research assistant measured the cardiovascular dependent variables with an Omron HEM-790IT1 (Ahmad et al 2012) automatic BP reader (Omron Healthcare, Inc, Bannockburn, IL) on the left arm at 5 and 7 minutes (time points 1 and 2, respectively). Thereafter, the physiotherapist applied light touch to the participants assigned to the placebo and PA pressures to those assigned to the experimental group. PA pressure was applied with the thumbs placed over the right C6 segment (Maitland et al 2005), and gentle pressure was applied by the therapist until movement was sensed, or until the participant reported a slightly unpleasant pain with a numeric pain rating scale of less than 2 (0= no pain, 10= excruciating pain). Ten seconds of the PA pressure were performed, with 10 seconds rest between sets for a total of 5 sets (Yung et al., 2014). During the first and fifth sets (time points 3 and 4, respectively), the assistants reassessed the dependent variables and repeated this at 2 and 4 minutes after the fifth set (time points 5 and 6, respectively). For data analysis, the averages of time points 1 and 2, 3 and 4, 5 and 6 were considered as: baseline, during-intervention, and post follow-up respectively. During-intervention, the therapist provided 15 oscillations of PA pressures per set lasting 10 seconds; this yielded a rate of application of 1.5 Hz (Yung et al 2014). The primary investigator is the only physiotherapist providing the intervention for all participants. This therapist has over 24 years of clinical experience, has undergone manual therapy fellowship training and is board-certified as an orthopaedic clinical specialist.

2.1 Sample Size

Using pilot data to perform the sample size calculation, the anticipated within-group differences in mean ± SD HR was 2.4 ± 3.0 bpm. If powered at 80% and targeting a statistical significance of .05, this process indicated that the required number of participants for each group in a paired-design study was 15 (Machin et al., 1997). Thus, we chose a sample size n=22 (n=44 in total) large enough to achieve high power for the primary outcome to allow for precise estimation of differences between baseline and follow-up periods.

2.2 Statistical Analysis

All the outcome data were checked for normality. Descriptive statistics, including frequency counts for categorical variables and means and standard deviations were calculated to summarize the data. Baseline characteristics were compared between groups using independent t tests for continuous data and chi-squared tests for categorical data to assess the adequacy of the randomization. The primary aim (effects of treatment on HR, SBP and DBP) was examined using multilevel mixed-effect modeling for repeated measures, adjusting for baseline values by entering treatment, time, and baseline values (age, gender and body mass index or BMI) as covariates. Separate analyses were performed on: HR, SBP and DBP as the dependent variables. 2-way interaction (treatment group by time) was also examined. Pairwise comparisons using a t-test with a Bonferroni adjustment were further conducted to identify differences between baseline and follow-up periods. All statistical analysis was conducted in R-statistical package (www.r-project.org). The fits of mixed model were done using function lme of the nlme package for the R environment of version 3.0.3. Statistical significance of $p < 0.05$ was considered to be relevant. Given the effect sizes, we performed post hoc power calculations to re-examine our power.

3. RESULTS

All data demonstrated a normal distribution based on the Shapiro-Wilk test for normality; therefore, no further transformation was required. Mean ages (SDs) of the participants were 24 (3.7) years in the PA group and 23.6 (2.3) years in the placebo group. Baseline characteristics between the groups were similar for all variables (P>0.05) (Table 1). A total of 44 enrolled participants completed the follow-up (Figure 1). All participants denied any adverse (n=0) and/or side effects (n=0) during the follow-up periods of 2 weeks and 4 weeks.

A mixed-effect model of repeated measure analysis showed no significant between-group differences for HR (Figure 2) and DBP (Figure 4). On the contrary, the averaged total HR, regardless of the groups, showed a statistically significant change over time (p-value=0.0043 in Table 2). The overall group-by-time interaction for the mixed-model was statistically significant only for SBP (p-value=0.0105). The ad-hoc pair-wise comparison further revealed that this was driven by the significantly different changes from baseline to during-intervention between groups (p-value=0.003 in Figure 3). In detail, the PA group had significantly reduced SBP from baseline to during- intervention while the placebo group had slightly increased SBP (p-value=0.003 in Figure 3). The between-group differences were no longer significant at post follow-up. Males had statistically higher SBP than females overall (p-value=0.0027 in Table 2).

A post-hoc power calculation was performed to assess the risk of a Type II error. The data used for the power calculation for between-group differences (mean [SD]) were the observed primary results to that seen in Table 2. A post-hoc power-calculation (based on unpaired t-test) revealed that with n = 51 (n=102 in total) and n=2271 (n=5542 in total), alpha = 0.05, and power=80%, a small effect size of 0.09 and 0.01 (assuming 1.25[3.16] vs 1.56[3.59] for changed HR and 0.75 [2.64] vs. 0.72 [2.25] for changed DBP, respectively) would have been detected if present. In detecting between-group differences of changed SBP, this study had a power of 77% to detect a moderate effect size of 0.93 (2.95 [3.11] vs. -0.72[4.66]).

4. DISCUSSION

The main finding of this study is that JM performed with a distinctive dose compared to placebo, led to an immediate transient reduction in SBP, implying a sympatho-inhibitory effect. Thus, this disparate result contrasts with the prevailing theory that JM produces sympatho-excitatory effect (Kingston et al., 2014). Though we did not directly compare dosage in this study, we postulate that the dissimilar dosing employed in our study (relative to the dosage in numerous previous studies) may largely explicate the divergent results. It is noteworthy that in practically all spinal JM studies (Kingston et al., 2014), the most widespread dosage employed was 60 seconds of JM followed by a 60-second rest. Conversely, the current study, with resultant sympatho-inhibitory cardiovascular effects akin to a previously reported study (Yung et al., 2014), employed an oscillatory technique with an alternative dosage of 5 bouts of 10 seconds, with 10 seconds rest in between each bout. Nevertheless, this represents a substantial reduction in the duration of each bout and the rest time between bouts. Furthermore, the total duration and the total rest time are greatly reduced compared to the other conventional dosages implying that the dosage of spinal mobilization may be a potential factor for manual therapists to consider as it pertains to the resultant BP response. Other than duration, there could be other variables (i.e. force, sampling of asymptomatic participants, etc.) that may explain the sympathoinhibitory results. The optimal dose for any one particular individual is unknown at this time.

A recent systematic review of Kingston et al. (2014) concluded that spinal JM largely leads to sympatho-excitation as the dominant paradigm of neurophysiological mechanisms underlying pain relief. Kingston el al. (2014) cited only 1 study that utilized the PA technique in patients with neck pain (Sterling et al., 2001), whereas the present study examined the effects in a healthy sample. Moreover, only 2 of the included studies assessed BP response (McGuiness et al., 1997; Vicenzino et al., 1998); of these 2 studies, only one (McGuiness et al., 1997) employed a similar technique (central, not unilateral, PA technique) in pain-free adults that demonstrated a sympatho-excitatory response. Therefore, due to limited high-quality evidence, it is still indeterminate whether the sympathetic response to spinal mobilization is analogous in both

healthy and symptomatic subjects and whether the response is technique-dependent or dosage dependent.

Additionally, there are other JM studies that have explored various parameters resulting in findings that are also dissimilar with the emerging theory that spinal JM results in a sympatho-excitatory response. Chiu and Wright (1996) demonstrated a significant difference in sympathetic effects based on the rate of the JM delivered, with a faster rate (2 Hz) resulting in greater increases in skin conductance than a slower rate (0.5 Hz) and a control condition. Research involving the use of thrust manipulation techniques of the cervical spine has demonstrated a sympatho-inhibitory response while thoracic spine manipulation has shown a sympatho-excitatory response (Welch and Boone, 2008). The delivery of thrust manipulation primarily differs from non-thrust mobilization in that thrust manipulation utilizes both a higher rate and also a shorter duration. While high velocity thrust techniques may have varying effects when compared to non-thrust mobilization, this evidence is in agreement with our findings of sympatho-inhibitory effects while mobilizing the cervical spine; and also conflicts with the emerging theory that sympathetic effects are the same irrespective of the level of the spine mobilized. Finally, research using sustained spinal mobilization (Moulson and Watson, 2006; Moutzouri et al., 2012) has reported no significant change in skin conductance compared to controls, supporting the theory that the oscillatory nature of JM is central to the sympathetic response. Hence, if the JM rate and the JM oscillation have been shown to have contradictory effects on the observed sympathetic response, then there would be reason to suspect that the dosing may also be a vital factor for the physiotherapist to consider.

Nonetheless, the precise modus behind the hypoalgesic effects of manual therapy has not been fully characterized. One commonly held notion is that JM activates a descending pain inhibitory system originating in the periaqueductal grey area (PAG) (Vicenzino et al., 1998). Determinants of BP may also be under at least partial control of the PAG through its effect on peripheral vascular control (Vicenzino et al., 1998). While these effects are posited to be sympatho-

excitatory in nature, the various interactions between the sympathetic nervous system and pain are still not fully understood (Fechir et al., 2012). Therefore, it may be possible to experience BP-related hypoalgesia with a drop in SBP versus the more traditionally expected increase in BP. This possibility is one reason why monitoring BP changes during and after the delivery of the mobilization technique requires further investigation.

Notably, some normotensive patients can have an upsurge in resting SBP in response to acute neck pain. Moreover, the evidence also suggests that in the case of chronic pain, the typical inverse relationship between resting blood pressure and pain sensitivity may be reversed. Thus, applying the typical dosage of mobilization may potentially result in a sympatho-excitatory response, further increasing resting SBP and therefore resulting in an undesirable and possibly dangerous cardiovascular effect. Conversely, this study demonstrated that the alternative dosing regimen could result in a decrease in SBP. Henceforth, this distinctive dosing may be safely considered for research in those with a new onset spike in resting SBP resulting from an acute pain episode. Similarly, preventing the development of chronic pain by producing a desirable reduction in pain and BP through JM during acute pain may be another beneficial consequence and warrants further exploration. In the chronic pain population, where there may be an increased risk for hypertension, an alternate model of pain modulation via a sympatho-inhibitory pathway may offer a safe alternative.

Remarkably, recently published guidelines for examination of the cervical spine suggest identifying vascular risk factors and evaluating cardiovascular vital signs in patients with neck pain in order to screen for potential cervical arterial dysfunction (Rushton et al., 2014). Consequently, the concern over the possible presence of increased BP in patients with neck pain has led some to question the safety of JM in this population. While a transient increase in BP in normotensive individuals would be acceptable, this response would be potentially alarming in hypertensive individuals. Therefore, a different dosage or technique is needed for

those individuals who present with an increased BP and this modified dosage may be an appropriate and safe option due to its proposed sympatho-inhibitory effects.

Heretofore, the results obtained from this study seem to support our theoretical model of a possible dichotomous response to spinal mobilization. Whereupon, the dosage may be a possible factor when considering different mechanisms underlying the cardiovascular effects of spinal mobilization. Hence, this new knowledge may serve to promote further investigations into the implications of future researcher's direct comparison of dosage parameters. If future studies comparing these disparate JM dosages result in two divergent BP-related neurophysiological mechanisms, the nuanced dosages could be utilized in two different potential clinical scenarios. Ordinarily, the traditional dosage with its sympatho-excitatory effects may be useful for the normotensive individual while the new dosage with its sympatho-inhibitory effects may be helpful for those who are typically normotensive, but had a recent spike in SBP in response to acute pain. Nevertheless, this should foster continued exploration of what constitutes optimal dosage of JM for a varied BP profile.

Our study has some limitations, namely: (1) we did not compare unilateral PA with different oscillatory dosage regimens so we cannot determine that our results are conclusively based on dosage; (2) we did not use the same dosage to directly compare unilateral PA from AP so we cannot conclude that the choice of technique is not as crucial as the dosage; (3) we did not perform PA on normotensive participants who recently had a spike in resting SBP as a response to acute pain to determine if the cardiovascular response is similar to the response obtained in pain-free subjects; (4) this study was insufficiently powered for some outcomes; (5) there may be other dose variables such as mobilization force that were not controlled in the study; and (6) we did not use a crossover design which may have made the study more robust.

5. CONCLUSION

This study demonstrated that utilization of an alternative dosing regimen with cervical JM compared to placebo could result in a small, short-lived decrease in SBP. Performing PA JM in the cervical spine may result in an immediate and transient SBP drop (not exceeding the minimal detectable change) in pain-free adults, which contrasted from the increase in SBP that was found in the placebo group. These results may also serve as values that may be used for comparison to those with neck pain in future research.

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FIGURE 1: Flow Diagram

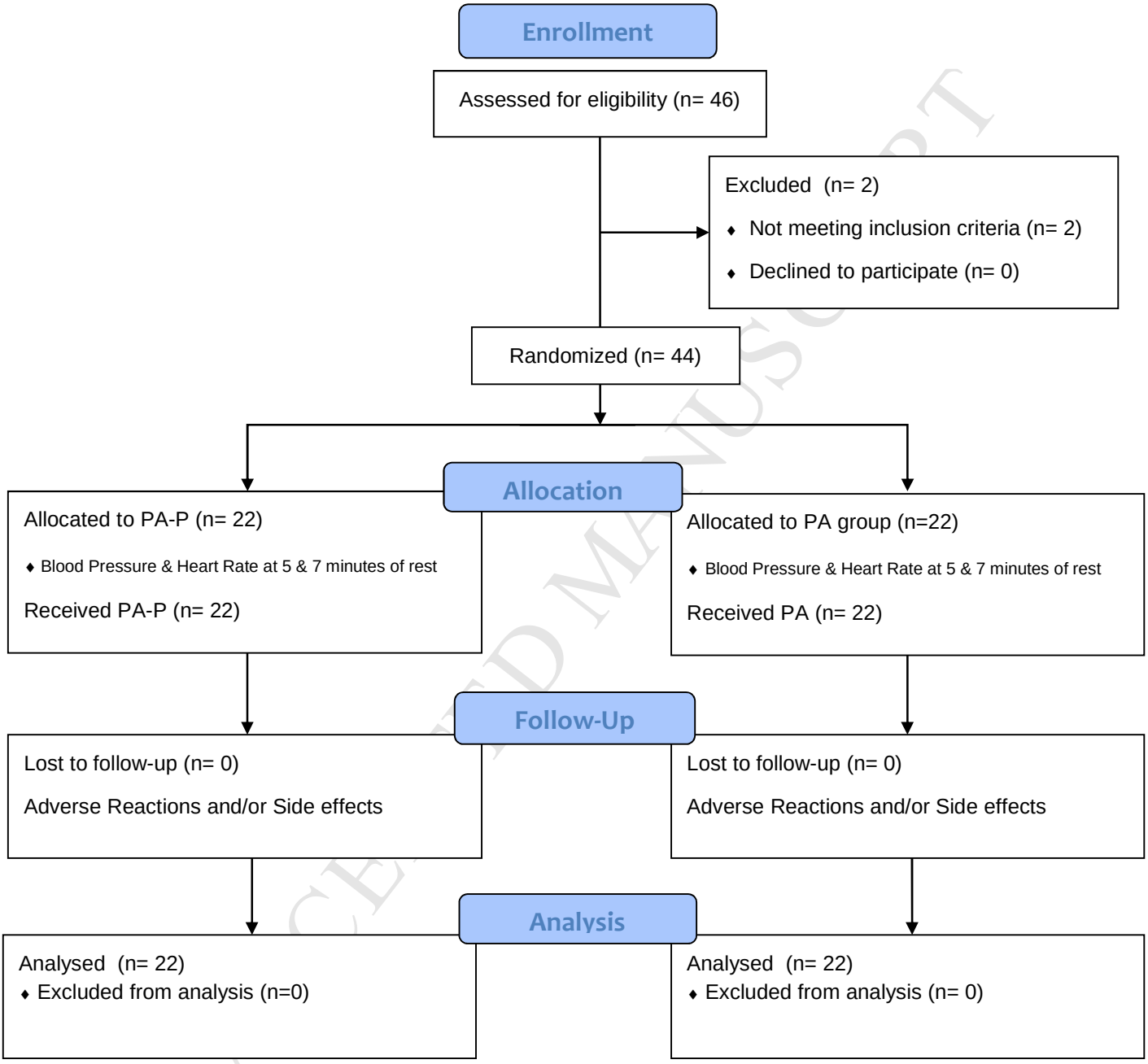


TABLE 1. Descriptive comparisons between unilateral posterior-to-anterior (PA) glides and placebo (PA-P)

		PA Group (n=22)	PA-P Group (n=22)	*P* Value
Gender *n* females (%)		9 (40.9%)	9 (40.9%)	*1***
Age, years		24.00 ± 3.66	23.63 ± 2.34	0.6972*
BMI		23.55 ± 3.34	24.17 ± 2.79	0.5077*
Heart rate	Baseline	60.13 ±11.64	63.70 ±12.48	0.3326*
	During	58.88 ±11.07	62.14 ±11.62	0.3477*
	Post	60.23±10.87	64.07±12.39	0.2807*
SBP	Baseline	110.61±10.61	111.43± 8.60	0.7802*
	During	107.65±11.31	112.15± 10.25	0.1743*
	Post	108.70±11.38	110.95±8.79	0.4675*
DBP	Baseline	66.95± 7.84	66.36± 6.30	0.7845*
	During	66.20±7.88	65.63±5.51	0.7833*
	Post	67.00±7.52	66.45±5.91	0.7906*

Values expressed as mean ± SD, except where otherwise indicated.
* t-tests ** chi-squared test

TABLE 2. Changed heart rate, systolic blood pressure and diastolic blood pressure from baseline comparison between PA and PA-P groups

Outcomes	Treatment	Baseline to During	Baseline to Post	p-value by MEM ANOVA			
				Between-Group	Time	Group×Time	Gender
Changed HR	PA PA-P	1.25±3.16 1.56±3.59	-0.09±3.55 -0.36±4.15	0.2957	0.0043	0.8508	0.0643
Changed SBP	PA PA-P	2.95±3.11 -0.72±4.66	1.90±4.76 0.47±3.77	0.3591	0.0895	0.0105	0.0027
Changed DBP	PA PA-P	0.75±2.64 0.72±2.25	-0.04±3.15 -0.09±3.03	0.7801	0.1143	0.9986	0.6665

Data displayed as mean±SD;
Abbreviation: MEM mixed-effect model for repeated measured analysis adjusted for age, gender and BMI; ANOVA analysis of variance

Figure 2. Mean heart rate at each time point.

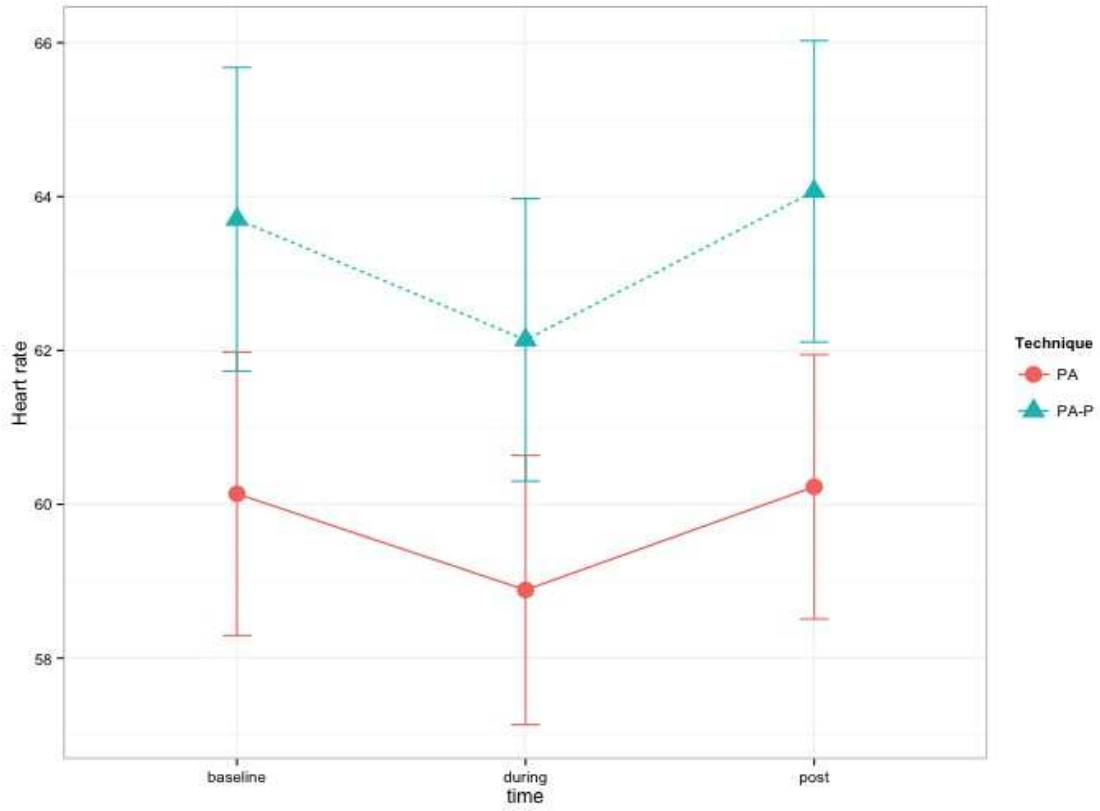


Figure 3. Mean systolic blood pressure at each time point. *Indicates a significant difference between groups followed by a post hoc Bonferroni's multiple comparisons.

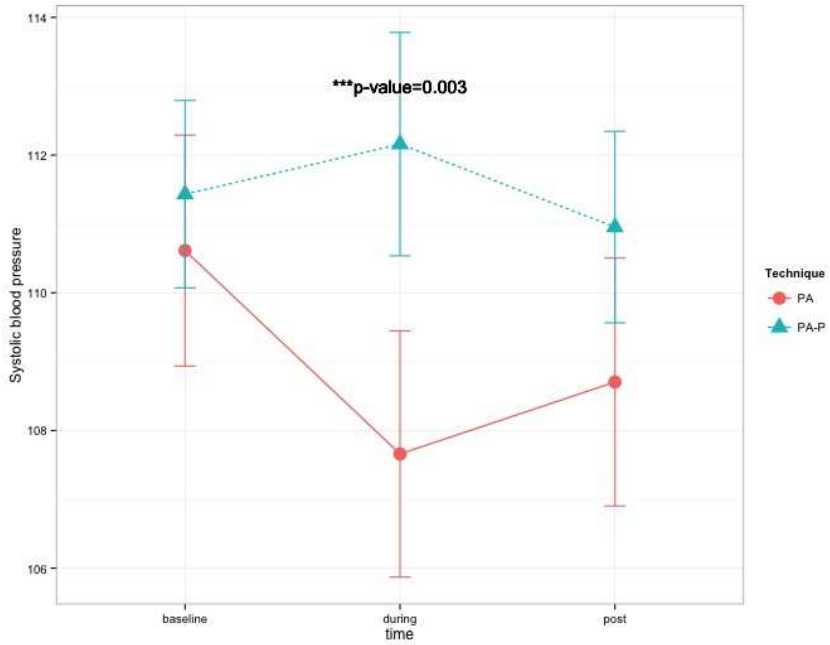
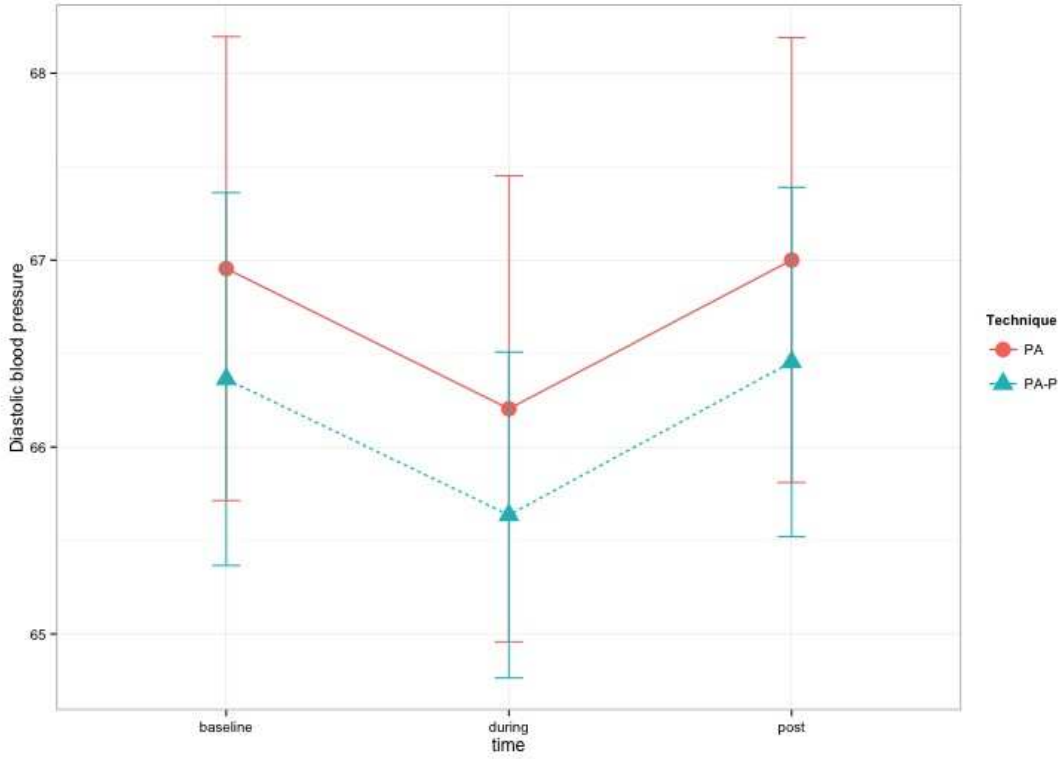


Figure 4. Mean diastolic blood pressure at each time point.



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Highlights

- The neurophysiological system that alters pain overlap with blood pressure.
- Following acute pain, the resting SBP may increase in some normotensive adults.
- Sympatho-excitation from usual JM dosage increasing SBP may be deleterious.
- It is essential to explore other JM dosing regimen to possibly decrease SBP
- The alternative JM dosage resulted in decreased SBP in normotensive adults vs placebo.