Differential Patient Responses to Spinal Manipulative Therapy

and their Relation to Spinal Degeneration and

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Arnold Y. L. Wong, Eric C. Parent, Sukhvinder S. Dhillon, Narasimha Prasad, Dino Samartzis, Gregory N. Kawchuk

Department of Physical Therapy,

University of Alberta,

Edmonton, AB, Canada.

arnold.wong@polyu.edu.hk

PURPOSE: Our prior study revealed that people with non-specific low back pain (LBP) who self-reported a > 30% improvement in disability after SMT demonstrated significant post-treatment improvements in spinal stiffness, dynamic muscle thickness and disc diffusion, while those not having self-reported improvement did not have these objective changes. The mechanism underlying this differential post-SMT response remains unknown. This exploratory secondary analysis aimed to determine whether persons with non-specific LBP who respond to spinal SMT have unique lumbar magnetic resonance imaging (MRI) findings compared to SMT non-responders.

METHODS: Thirty-two participants with non-specific LBP received lumbar MRI before and after SMT on Day 1. Resulting images were assessed for facet degeneration, disc degeneration, Modic changes and apparent diffusion coefficient (ADC). SMT was provided again on Day 4 without imaging. SMT responders were classified as having a ≥ 30% reduction in their modified Oswestry disability index at Day 7. Baseline MRI findings between responders and non-responders were compared. The associations between SMT responder status and the presence/absence of post-SMT increases in ADC values of discs associated with painful/non-painful segments as determined by palpation were calculated. In this secondary analysis, a statistical trend was considered as a P value between 0.05 and 0.10.

RESULTS: Although there was no significant between-group difference in all spinal degenerative features (e.g. Modic changes), SMT responders tended to have a lower prevalence of severely degenerated facets (P = 0.05) and higher baseline ADC values at the L4–5 disc when compared to SMT non–responders (P = 0.09). Post hoc analyses revealed that 180 patients per group should have been recruited to find significant between–group differences in the two features. SMT responders were also characterized by significant increases in post–SMT ADC values at discs associated with painful segments identified by palpation (P < 0.01).

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CONCLUSIONS: The current secondary analysis suggests that the spines of SMT responders appear to differ from non–responders with respect to degeneration changes in posterior joints and disc diffusion. Although this analysis was preliminary, it provides a new direction to investigate the mechanisms underlying SMT and the existence of discrete forms of treatment–specific LBP. These slides can be retrieved under Electronic Supplementary Material.

KEYWORDS: Apparent diffusion coefficient; Degeneration; Facet joint; Low back pain; Spinal manipulative therapy

TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT01761838

From the FULL TEXT Article:

Introduction

Low back pain (LBP) is the most common disabling health condition in the world. [1] Despite its high prevalence, approximately 90% of these cases are diagnosed as nonspecific LBP due to unknown aetiology. [2] Accordingly, patients with non–specific LBP are thought to be a heterogeneous collection of various aetiologies [2] as demonstrated by variable responses to any given intervention. [3–7]

Notably, spinal manipulative therapy (SMT) is a common treatment for non–specific LBP that has shown a range of therapeutic effects. [3–5] Our recent study confirmed this variation in outcomes. Some participants demonstrated clinically significant improvements in LBP–related disability after 1 week of SMT treatments displayed post–SMT decreases in spinal stiffness, increases in lumbar multifidus contraction and increases in water diffusion at the L4–5 and L5–S1 discs. [3] Conversely, no such changes were observed in SMT non–responders, untreated non–specific LBP controls or untreated asymptomatic controls. [3] Divergent physical and clinical responses in patients with non–specific LBP following an identical SMT application highlight the importance of matching patient subgroups to the right LBP intervention. [8] Importantly, these findings also offer a unique opportunity to identify whether the differential treatment responses arise from patients with distinct underlying lumbar problems—a long–held premise with little empirical evidence.

Since our prior results have shown that only SMT responders demonstrated post–treatment improvement in water diffusion in multiple lumbar discs [3], it may imply that SMT non–responders may display other spinal degenerative features (e.g. vertebral subchondral bone marrow lesions) that differ from SMT responders. [9–13] Additionally, because post–SMT improvement in disc diffusion may benefit disc health and repair [13, 14], an exploration of the association between post–SMT improvement in disc diffusion at certain segments (especially discs associated with painful segments as determined by palpation) and corresponding clinical improvements would help determine whether post–SMT enhancement of diffusion in certain discs on magnetic resonance imaging (MRI) was related to improved clinical outcomes.

Thus, our primary objective was to perform an exploratory secondary analysis of our previous data to determine whether SMT responders differed in their lumbar degeneration status from SMT non–responders, which might explain differential therapeutic responses of patients with LBP after SMT. An additional objective was to determine whether the presence/absence of increase in disc diffusion of painful segments following the first application of SMT was related to SMT responder/non–responder status after 1 week. It was hypothesized that SMT non–responders displayed significantly more degenerative spinal features than SMT responders. It was also hypothesized that an improvement in disc diffusion of pain segments after the first application of SMT was associated with favourable clinical improvements after 1 week.

Materials and methods

Study design and participants

We performed an exploratory secondary analysis of a prospective non–randomized clinical trial investigating post– SMT differential responses of individuals with LBP [3] (ClinicalTrials.gov identifier: NCT01761838). Participants aged 18–60 years with non–specific LBP were recruited from multidisciplinary settings. All enrolled participants had a minimum LBP intensity of 2 on the 11–point numeric pain rating scale and at least 20% on the modified Oswestry Disability Index (mODI). [3] Exclusion criteria included but were not limited to: prior lumbosacral surgery, prior SMT within the past 4 weeks, scoliosis, pregnancy, spinal fractures/ tumours or any contraindications for MRI. [3]

To minimize the risk of unknowingly recruiting an excessive number of SMT responders or non–responders, we attempted to balance these groups by employing a clinical prediction rule for identifying potential SMT responders during enrolment. [15] Individuals with ≤ 2 items in the clinical prediction rule were recruited as potential SMT non–responders, while those with ≥ 4 characteristics were recruited as potential responders (“Appendix 1”). [3, 4] Individuals with exactly three characteristics were excluded as per prior research. [3, 4] All participants gave written informed consent for the study approved by the institutional research ethics board.

Procedure

Figure 1

Thirty–two participants with LBP attended three morning sessions in 1 week (Figure 1). On session 1, participants provided demographics and completed the mODI. The lumbar spine was palpated at the spinous processes to identify painful and non–painful segment(s). [16] The cephalic and caudal intervertebral discs (IVDs) associated with the painful segment were noted. Additionally, participants underwent lumbar MRI (L1–S1), spinal stiffness assessments and multifidus ultrasonography before, and after, the application of SMT in the first session. [3] The mean time between scans was 1 h. On session 2 (3–4 days later), participants repeated these procedures but without MRI. On session 3 (Day 7), only the mODI score, spinal stiffness and multifidus function were completed; no SMT was provided. Participants were then dichotomized as SMT responders and non–responders based on ≥ 30% and < 30% reduction in baseline mODI scores. This cut–off is recognized as the minimal clinically important improvement in LBP disability [17] although different minimal clinically important improvement values have been suggested by different studies. [18–20]

Spinal manipulative therapy

Participants received standardized SMT described elsewhere. [3] Briefly, it involved a long–lever application of a posteroinferior thrust to the pelvis (“Appendix 2”). During sessions 1 and 2, a maximum of two SMT applications were allowed for each side of the participant.

Imaging

Table 1

Participants' lumbar spines were scanned by a 1.5 Tesla MRI unit (MAGNETOM Symphony, Siemens Medical Solutions) using multi–element spine coils. The pre–SMT imaging protocol included sagittal TI– and T2–weighted turbo spin echo, axial T2–weighted turbo spin echo, sagittal STIR sequence and sagittal diffusion–weighted imaging (DWI) sequences (Table 1), while post–SMT imaging only involved DWI. [3] Sagittal DWI were acquired using a single shot, dual spin echo, echo–planar imaging acquisition with multi–element spine coils and abdominal coils. The image processing system of the scanner constructed mean apparent diffusion coefficient (ADC) maps.

Grading of MRI findings

A certified radiologist, blinded to the ADC findings, reviewed each participants' imaging and provided scoring for: facet joint degeneration, IVD degeneration and Modic changes (MCs) between the L3 and S1 segments. These segments were chosen as LBP was commonly noted in the lower lumbar spine. [21, 22]

The facet joint degeneration at L3–L5 levels was graded by a validated 4–point scale having a high intra–observer reliability (kappa 0.70–0.77) and clinical relevance. [23] Facet degeneration was graded based on joint space, the presence of osteophyte, articular process hypertrophy, subarticular erosion and subchondral cyst. [23] A zero score denoted no degeneration, while 3 represented severe degeneration. [24] Disc degeneration at all lumbar levels was graded by the 5–point Pfirrmann grading system that is based on disc height, homogeneity of the disc structure, differentiation between nucleus and annulus, and T2-weighted signal intensity. [25] This grading system has demonstrated excellent intra-rater reliability (kappa from 0.84 to 0.90). [25] Higher grades indicate more severe degeneration.

The MCs of vertebrae were graded by a method with substantial to almost perfect intra-observer reliability (kappa from 0.77 to 1.00) [26]. Specifically, type I MC (fibrovascular replacement of subchondral bone) was characterized by decreased T1 and increased T2 signal intensity. [27] Type 2 MC (endplate fissures and fatty replacement of subchondral bone) showed hyperintense T1 and isointense/hyperintense T2 signals. [27] Type 3 MC (sclerosis of subchondral bone) appeared as hypointense T1 and T2 signals. [27] If multiple types of MCs coexisted at the endplate/subchondral bone, it was labelled as mixed type 1/2 or 2/3 MC. The locations and sizes (endplate area, maximum height, volume or anteroposterior diameter) of MCs were recorded. [28, 29]

ADC measurements

An examiner blinded to the radiologist's grading used a customized programme to measure mean ADC values (ADC mean) of five lumbar discs on the midsagittal ADC map. Notably, a 40 mm2 circular region of interest (ROI) was placed in the central, nuclear portion of a disc on the midsagittal ADC map to minimize the noise signals from adjacent vertebral structures. The ADC mean of a disc was estimated from signal intensity within the ROI. If the diameter of the ROI exceeded the disc height, the disc was excluded from analysis. [3] A high ADC value represents higher IVD diffusion. [13]

Intra-observer reliability of assessments

Three weeks after initial imaging, the radiologist and the examiner independently repeated the grading of MRI findings and ADC measurements on the scans of randomly selected participants. Both readers were blinded to all measurement results.

Statistical analysis

The exploratory, secondary analyses of underpowered data were conducted using SPSS 22.0 software (IBM, Armonk, NY). As some categories of the MRI findings showed low prevalence of specific grades (< 10%) (e.g. type 3 MC), each variable was dichotomized to calculate the intra-observer reliability using kappa analysis. [30] Specifically, Pfirrmann grading was dichotomized into “no/mild disc degeneration” (grade 1–3) and “severe disc degeneration” (grade 4 or 5). [31] MC was dichotomized as “no” and “yes” (regardless of types or locations). Facet joint degeneration was dichotomized as “no/mild degeneration” (grade 0 and 1) and “severe degeneration” (grade 2 and 3). [32] Kappa coefficients were interpreted as follows: poor (≤ 0), slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) and excellent (0.81–1.00). [33] The intra-observer reliability of ADC measurements was reported elsewhere [3] and demonstrated excellent intra-class correlation coefficients (ICC3,1) estimates (0.97–0.98) (“Appendix 3”). [3, 34]

Chi-square/Fisher's exact tests assessed differences in the frequency of dichotomized MRI findings between responders and non-responders. Demographic data and baseline ADC mean of all lumbar IVDs in responders and nonresponders were checked for normality using Shapiro–Wilk tests. If continuous data were not normally distributed, Mann–Whitney U tests would replace independent t tests for between-group comparisons. The effect sizes of all betweengroup comparisons were calculated. [35] Additionally, to determine the baseline ADC mean cut-off of each IVD that could differentiate responders and non-responders [36], area under the curve (AUC) of the receiver operating characteristic curve and Youden index were used. [34, 36] An AUC value of 0.5 indicates that the baseline ADC mean of a disc is no better than chance to distinguish between responders and non-responders, while an AUC of 1.00 represents the baseline ADC mean that could always identify the responders. [34] The cut-off was chosen if Youden index value (J = maxc [Se(c) + Sp (c) – 1]) was maximum, where Se and Sp were the probability of truly identifying responders and non-responders, respectively, at a given cut-off (c). [36]

The differences in post-SMT changes in ADC mean of IVDs associated with painful/non-painful segments between responders and non-responders were examined by separate Chi-square tests. To dichotomize the post-SMT changes in ADC mean into increase or no change/decrease in ADC mean, values of the minimal detectable change at the 95% confidence interval (“Appendix 4”) [37] derived from intraobserver reliability of ADC measurements at the respective disc levels were used as the cut-offs. Cramer's V tests were used to estimate the strength of the association. Cramer's V values were interpreted as weak (< 0.10), moderate (0.11–0.33) and strong (> 0.30) [38]. The significance level was set at 0.05 for all tests. For this exploratory secondary analysis, a P value between 0.05 and 0.10 was considered as a trend towards significance.

Results

Table 2

Figure 2

Figure 3

Figure 4

Table 3

Table 4

Based on mODI scores, 15 participants were classified as SMT responders and 17 as non-responders. The baseline demographics of these two groups were comparable (Table 2). The intra-observer reliability of the various lumbar degeneration grading was excellent (κ = 0.80–0.84) (“Appendix 3”). [33]

Responders' and non-responders' MRI findings

Compared to SMT responders, SMT non-responders displayed a trend of higher prevalence of severely degenerated facet joints (χ2 = 3.86, P = 0.05, Cramer's V = 0.14) (Figure 2). From the post hoc analysis using G \* Power program [39], 180 participants per group should have been recruited to detect a significant between-group difference in facet joint degeneration (Power = 0.80, α = 0.05). There was no statistically significant between-group difference in the prevalence of IVD or MC grading. While most IVDs in both subgroups were not degenerated, more degenerated discs were found at the L4–5 and L5–S1 levels (Figure 3). Modic changes were observed in 46.7% and 58.8% of responders' and non-responders' endplates, respectively. For responders, the prevalence estimates of types 1, 2 and 3 MCs in endplates were 9.5%, 4.8% and 1.0%, respectively (Figure 4). Similarly, type 1, type 2, type 3 and mixed type 1/2 MCs were noted in 6.7%, 5.0%, 0.0% and 5.9% of non-responders' endplates, respectively (Fig. 4). The anterior superior endplate showed the highest relative frequency of MCs (33.3% to 34.5%) in both subgroups although it did not significantly differ from other locations. The majority of the observed MCs involved only endplates (88.9% in responders, 68.9% in non-responders).

Baseline ADC mean of responders and non-responders

Five out of 160 IVDs were excluded from the ADC measurements because the disc space was smaller than the ROI diameter. All the excluded discs were from five non-responders at L1–2 (n = 2) and L4–5 (n = 1) and L5–S1 discs (n = 2). There was no significant difference in ADC mean of all intervertebral discs between responders and non-responders. However, compared to responders, non-responders had a trend of lower estimated baseline ADC mean of the L4–5 disc (U = 78.00, P = 0.09, r = 0.30) (Table 3). The post hoc analysis revealed that a sample size of 43 per group should have been recruited to detect a significant between-group difference of this magnitude (Power = 0.80, α = 0.05). Similarly, while AUCs for baseline ADC mean of discs at each level were not statistically significant, the AUC of the L4–5 disc was 0.70 (95% CI: 0.50–0.89; P = 0.07). Specifically, patients with baseline ADC mean higher than 2.07 × 10–3 mm2/s at the L4–5 disc were more likely to be responders (sensitivity = 0.71; specificity = 0.68).

Comparing post-SMT ADC mean changes in discs at painful/non-painful segments

between responders and non-responders

Compared to non-responders, a significantly higher proportion of discs identified as painful in responders demonstrated immediate post-SMT increases in ADC mean (Cramer's V = 0.50, P < 0.01) (Table 4). Conversely, both responders and non-responders did not show significant differences in the patterns of post-SMT changes in ADC mean of discs associated with non-painful segments (P > 0.01) (Table 4).

Discussion

While the current secondary analysis has revealed no statistically significant differences in spinal structural features between SMT responders and non-responders, lumbar degeneration status appears to be related to post-SMT treatment outcomes. Compared to SMT responders, the nonresponders demonstrated a trend of a higher prevalence of severe facet degeneration (P = 0.05) and relatively lower baseline ADC mean of the L4–5 disc (P = 0.09). Given the exploratory nature of our analyses, it is important to consider all potential findings that may explain mechanisms underlying the differential responses between SMT responders and non-responders. Our results suggest that spinal degeneration (especially the discs) may be a potential treatment effect modifier for SMT in patients with non-specific LBP although further studies are warranted to test this hypothesis.

Distinct baseline ADC mean and post-SMT disc diffusion responses were noted between responders and nonresponders. Our current data suggest that ADC mean of IVDs may be more sensitive to the microstructural intradiscal changes that may not be quantified by qualitative grading on MRI. [40] Since a lower ADC mean indicates greater disc degeneration [13, 41], our findings suggest that non-responders may have more degenerated L4–5 discs, which may be sources of LBP. [42] A prior ovine study has found that a spinal segment with a degenerated disc displays less movement during SMT as compared to a nondegenerated spine. [43] Such distinct mechanical responses may explain the differential SMT responses. Additionally, Vieira-Pellenz found that male LBP patients with degenerative discs who demonstrated greater increases in body height (a proxy of improved disc height) after a single session of SMT were associated with less LBP prevalence. [44] Given these results, further studies with larger sample sizes are warranted to determine the causal relations among spine degeneration, post-SMT mechanical responses and LBP.

Interestingly, our findings highlighted that responders were characterized by immediate post-SMT increases in ADC mean of discs associated with painful segments on session 1. This finding implies that favourable clinical outcomes arising from SMT may be partly due to improved diffusion of discs associated with painful segments. Since the significant relation between level-specific post-SMT increases in ADC mean of discs and improved clinical outcomes was only found in SMT responders, it corroborates the importance of conducting further studies to clarify the association between spinal degeneration and SMT outcomes, especially when SMT non-responders displayed a the trend of more lumbar degenerative features. Notwithstanding the strong association between post-SMT increase in ADC mean of discs on session 1 and clinical improvements on session 3, improved disc diffusion might not be the sole reason for the differential clinical responses of our participants. Since 26.8% of discs at the painful segments of the responders showed no change/decrease in the post-SMT ADC mean (Table 4), their clinical improvements may be related to the mechanical and/or neurophysiological effects of SMT on spinal tissues other than improved disc diffusion. Similarly, if IVDs were not the sole source of LBP or the dosage of SMT was insufficient to elicit significant clinical improvements in the non-responders, enhanced post-SMT disc diffusion would not improve clinical outcomes. Furthermore, SMT is unlikely to benefit non-biomechanical pathologies, e.g. inflammation of vertebral subchondral bone [45] or increased nociceptive innervation in IVDs/vertebral endplates. [46]

Additionally, our findings underscore the presence of treatment-specific types of LBP. As non-specific LBP is a constellation of heterogeneous conditions that have varied mechanisms of pain generation [47, 48], the application of a single LBP treatment to patients with non-specific LBP would be expected to result in diverse clinical outcomes as is the case in our work and that of others. [48, 49] Although there have been many suggestions as to why this diverse range of responses exist to a given treatment [50–53], this secondary analysis suggests that a selective response to a particular intervention does exist and has a potential physiological explanation consisting of distinct biological and biomechanical characteristics. Our findings indicate a novel research direction for investigating the influence of structural features in affecting treatment responses, which may guide certain clinical decision in future. However, it is not recommended to order routine MRI scans for the sole purpose of determining the application of SMT.

The current study has inherent limitations. First, as the current exploratory, secondary analysis was not powered for the comparison of MRI findings between responders and non-responders. As such, no statistically significant difference can be drawn, and our results should be interpreted with caution. Future research with a larger sample size is warranted to validate the current findings. Second, although SMT responders and non-responders were dichotomized based on a 30% decrease in baseline mODI scores at the third visit, the absolute change in mODI score of a SMT responder could be as small as 6 points if the participant's baseline mODI score was only 20 points. While 6 points were still larger than some suggested minimal detectable changes in patients with LBP (ranging from 3.2 to 5.2 points) [18], this value was much smaller than other suggested minimal detectable changes (15–19 points). [19] Therefore, some SMT responders' mODI improvements might not demonstrate minimal clinical important differences had other cut-off methods been used. Third, since the present study investigated the association between post-SMT changes in ADC mean of IVDs on session 1 and the clinical outcomes on session 3, the relation between serial changes in ADC mean of IVDs and the respective clinical outcomes remains unknown.

As prior research suggests that SMT may have a positive dose–response effect on clinical outcomes [54], it is conceivable that SMT may have similar cumulative effects on the disc diffusion changes. Future research should measure both the post-SMT ADC mean and clinical outcomes at successive time points to clarify this relation. Fourth, while our results appeared to suggest distinct MRI spinal findings in SMT responders and non-responders, MRI scans are rarely ordered in clinical practice for patients with non-specific LBP. Future studies should investigate whether differential spinal degenerative features exist in plain radiographs (i.e. X-rays) between SMT responders and nonresponders, which may inform clinical decision-making and further assist in more refined patient selection for further imaging assessments.

Conclusions

There was no significant difference in structural features between SMT responders and non-responders. However, SMT responders demonstrate a trend of a lower prevalence of severely degenerated facets and relatively high baseline ADC values of the L4–5 discs. Interestingly, SMT responders demonstrate post-SMT increases in apparent diffusion coefficient (ADC) values of discs associated with painful segments. These results suggest that SMT responses may be related to some underlying structural responses. Our findings provide a new hypothesis/direction for further investigating the underlying nature of the differential response to SMT, possible mechanisms of SMT and the existence of treatment-specific forms of LBP.

Appendix 1: Clinical prediction rule

Clinical characteristics of the clinical prediction rule for identifying people

who benefit from spinal manipulative therapy

Clinical characteristics Definition of a positive finding

1. Duration of the current Less than 16 days

episode of low back pain

2. Distal symptoms No symptoms distal to the knee

3. Fear avoidance beliefs Less than 19 points

questionnaire work subscale

4. Lumbar stiffness At least one lumbar segment is

determined to be hypomobile

by the examiner using a manual

posteroanterior spinal mobility

test

5. Hip internal rotation At least one hip with 35° or

range of motion greater as measured by an

inclinometer in prone

Appendix 2: Spinal manipulative therapy procedure

The supine participant crossed and put his/her fingers behind the neck. The clinician stood opposite to the side to be manipulated and side bent the participant's trunk towards the side of the pelvis to be manipulated, and rotated the trunk in the opposite direction. Then the clinician applied a highvelocity, low-amplitude thrust to the pelvis in a posteroinferior direction. The clinician delivered spinal manipulative therapy to each side at each given session. If the first attempt did not result in cavitation, a second spinal manipulation was allowed for each side. A maximum of two spinal manipulations would be given to each side within a session. In the current study, only two out of 64 sessions required a second spinal manipulation on the one side (one for responder and one for non-responder).

Appendix 3: Intra-observer reliability of the dichotomized degeneration variables

Appendix 4: Intra-observer reliability of apparent diffusion coefficient measurement

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