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Research Paper Review

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Changes in Biochemical Markers Following Spinal Manipulation

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ABSTRACT

INTRODUCTION: *The aim of this meta-analysis was to determine the effectiveness of spinal manipulation in influencing various biochemical markers in healthy and or symptomatic population.*

METHODS*: Electronic databases (n = 10) were searched (from inception till September 2016) and eight trials (325 participants) that met the inclusion criteria were included in the meta-analysis. Two authors independently extracted and assessed the risk of bias in included studies. Standardised mean differences for outcome measures were used to calculate effect sizes. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was used for assessing the quality of the body of evidence for each outcome of interest.*

RESULTS: *There was moderate quality evidence that spinal manipulation influenced biochemical markers. There was moderate quality evidence of significant difference that spinal manipulation is better (SMD -0.46, 95% CI - 0.93 to 0) than control in eliciting changes in cortisol levels immediately after intervention. There was also a low quality evidence that spinal manipulation is better than control at post-intervention in increasing substance-P (SMD -0.48,95%CI-0.87 to -0.1), neurotensin (SMD -1.8,95%CI-2.56 to -1.04) and oxytocin levels (SMD -2.61,95%CI-3.5to-1.72). However, low quality evidence indicated that spinal manipulation did not influence epinephrine (SMD 0.1,95%CI- 0.56to0.75) or nor-epinephrine levels (SMD -0.06,95%CI-0.71to0.6).*

CONCLUSION*: The current review found that spinal manipulation can increase substance-p, neurotensin, oxytocin and interleukin levels and may influence cortisol levels post-intervention. However, future trials targeting symptomatic populations are required to understand the clinical importance of such changes.*

ANALYSIS

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Background Information

There is a growing body of evidence demonstrating the efficacy of spinal manipulation (SM) for the treatment of low back and neck pain (1-4). While it has been demonstrated to be clinically effective, the exact mechanism through which SM exerts if effect remains uncertain. Generally, SM is believed to create a number of neurophysiological changes in the body by affecting the peripheral and autonomic nervous systems, as well as the endocrine system (5).

With respect to the sensation of pain, nociception at the site of injury is mediated by biochemical markers that are produced both locally and remotely, such as neurotensin, oxytocin and substance-P (SP), which transmit the signal from the area of injury to the nervous system (6). These biochemical markers are also related to the initiation of the inflammatory response at the site of injury, which leads to the production of proinflammatory and immunoregulatory cytokines and neurotransmitters such as tumour necrosis factor-alpha (TNF-α), interleukins (IL), endogenous opioids, hormones and catecholamines (7).

While it has been hypothesized that SM activates the release of biochemical markers from neural tissue, no systematic review has evaluated the strength of this evidence. The objective of the current systematic review was to determine the effects of SM on biochemical markers in humans and establish the level of evidence for changes in biochemical biomarkers following SM.

Pertinent Results:

- A total of 1217 citations were screened, with 45 potentially relevant articles fully assessed for eligibility.

- Eight trials were included in the final review (12-19). All studies were RCTs and a total of 325 subjects were included in these eight studies. The average age of study

participants was 26. Only one study (13) included participants with acute neck or thoracic pain.

- Four studies (12, 16-18) used thoracic manipulation (due to the proposed relationship to the autonomic nervous system). Two studies used cervical manipulation (13, 19). Two studies used both cervical and thoracic SM (14, 15). Typically, low velocity, low amplitude mobilizations were used as the sham procedure, or touch with no pressure was used as control.

- From the data extracted from the eight included studies, there was moderate quality evidence that SM was better than control in eliciting changes in biochemical markers. Specifically:

    1. There was low quality evidence from three studies (12, 14, 17) that SM is better at increasing SP levels immediately after intervention, but there was very low quality evidence at the short-term time point.

    2. There was low quality evidence from one study that SM was better than control at increasing neurotensin and oxytocin levels post-intervention (15).

    3. There was moderate quality evidence from three studies of a significant difference that SM is better than control in eliciting changes in cortisol levels immediately (13, 15, 19), however, there was low quality evidence of no significant difference at short-term.

    4. There was low quality evidence from one study of no difference immediately between SM and control on epinephrine and norepinephrine levels.

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CLINICAL APPLICATION & CONCLUSIONS

This review identified moderate level evidence supporting the use of SM in influencing biochemical markers immediately following the intervention. While the populations studied were mainly healthy subjects, these markers have important roles in the perception of pain and the inflammatory, healing and immune responses to injury (10, 20). Given the current challenges of managing pain using opioid medications, it is possible that non-drug interventions such as SM could have a valuable role to play in pain management (21, 22).

It is noteworthy that only one study included subjects with pain. Further, no patient-related or pain-related outcomes were assessed in the included studies. As such, it is not possible to comment on the clinical application of SM (as it pertains to biochemical markers), however, the authors noted its efficacy and effectiveness have been well documented previously.

Importantly, the reviewers noted implications for future research, including managing for covarying factors and examining the effects of SM on symptomatic subjects. Including patient-related outcomes may also allow for correlation between biochemical changes and clinical outcomes. Further, a broader age range of participants would also increase the generalizability of the findings, along with a longer assessment period. Lastly, the reviewers suggested it may be relevant to compare SM in different spinal regions (including the lumbar spine).

EDITOR'S NOTE: this line of work is essentially in its infancy, with very little data to go on, as has been discussed here. What we see in practice is patients who just feel better, both immediately after SM and over time as well. It will be interesting to see if research like this, as it progresses, can identify potential underlying mechanisms for these observed responses. It is worth noting that in many of the studies included in this review, the measurement of biochemical markers was recorded after only ONE treatment. It would be interesting to see what happens to these biomarkers over time when patients are under care – we just don't have this data at this point! Remember, sometimes research has not fully caught up to what we see in practice – this is a challenging area to study properly, without many chiropractic or manual medicine-based experts to conduct the work!

STUDY METHODS

- A bibliographic search was performed on ten databases from inception to September 2016. Additionally, grey literature and trial registries were searched.

- Randomized controlled trials (RCT) or controlled clinical trials that involved humans (no conditions on age, gender, pain) published in the English language were eligible for this review. Included studies must have investigated SM, and the intervention must have been provided by a physiotherapist, osteopath or chiropractor. The comparator could have been control, usual care, GP care, placebo, sham or other therapy. Outcome measures were biochemical markers (in any bodily fluid).

- Two authors independently screened titles and abstracts for inclusion.

- Two authors then independently assessed risk of bias using the Cochrane Collaboration tool (23). Studies were considered to have low risk of bias if the random sequence generation, allocation concealment and incomplete outcome data domains were adequately met.

- Two reviewers extracted data from included studies and built evidence tables.

- Meta-analyses were performed when possible at immediate (up to 30 minutes) and short-term (hours) time points. All outcomes were examined as a standardized mean

difference (SMD) and effect size and 95% confidence intervals were calculated for each treatment comparison.

- Overall quality of the evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (24).

STUDY STRENGTHS/WEAKNESSES

Strengths:

- The authors used a clearly defined research question with a thorough and systematic search.
- Independent screening of titles, abstracts and full texts.
- Only those trials assessed as being of high quality were included.
- Assessment of risk of biased was performed with a validated set of criteria.
- Two authors independently extracted the data from the included articles.
- The reviewers provided a thoughtful reflection regarding the strengths and weaknesses of the review.

Weaknesses:

- The primary limitation of this study relates more to the quality of the body of evidence than the methodology of the review itself.
- Although the authors used a validated tool to assess risk of bias, only three criteria were required for inclusion in the review.
- The sample sizes of the included studies were small.
- The included participants were young and healthy and thus limit the generalizability of the review.
- Only one included study provided data regarding harm/adverse events (16).
- Given the lack of symptomatic patients in all but one study, clinical correlations cannot be made.

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