
Design: Meta-analysis of clinical trials

PICOS:
- Patient population: Adults (18 or over) with one of three categories of neck pain
  - Neck pain without radicular findings, including whiplash, myofascial pain, degenerative changes, or no specific cause
  - Cervicogenic headache
  - Neck pain with radicular findings, including spinal stenosis or degenerative joint or disc disease
  - Some disorders were excluded: myelopathies or other long tract signs, headache not originating in or dominated by neck pain, and neck pain caused by other known specific conditions
- Interventions: Manipulation (high velocity low amplitude) directed at specific spinal segments (not necessarily cervical segments alone), and mobilization (low velocity, small or large amplitude passive movements, or neuromuscular techniques within the patient’s range of motion and under the patient’s control)
- Comparisons: A control such as placebo, adjunct treatment (such as ultrasound plus manipulation compared to manipulation alone), wait list or no treatment, any intervention other than manipulation/mobilization, one technique versus another technique, or one dose versus another
- Outcomes: Main outcomes were pain relief, function, disability, patient satisfaction, or quality of life, using either self-report or observer-based physical performance tests
  - Outcomes assessed during a standard physical examination, such as range of motion, motor strength, proprioception, and neurological tests, were excluded
- Study types: Randomized or quasi-randomized trials in full text or abstract form

Study selection:
- Databases included MEDLINE, EMPASE, the Central Cochrane register, CINAHL, and the Index to Chiropractic Literature
- Reference lists and personal communication with experts in the field were also searched for relevant articles
- Literature was searched through July 2009
- The Cochrane Risk of Bias tool, with a 12 point scale, was applied by two independent reviewers to classify studies into those with a low risk of bias (more than 6 points) and high risk of bias (scoring 6 points or fewer)
  - Authors recognized that studies could not blind the clinicians, and that very few patients could be blinded to treatment
  - Common avoidable sources of bias were failure to document concealment of allocation and/or compliance with treatment; most
studies also failed to ensure that co-interventions were balanced between groups

- Studies of high risk of bias were noted as such, but were not excluded from the analyses
- After assessment of risk of bias, other considerations for quality of evidence were assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system, which considers the consistency, directness, precision and reporting of studies
  - Quality of evidence ratings represent the judgment of the authors regarding the robustness of the results to the likely effects of new information from further research
    - High quality means that further research is very unlikely to change the confidence in the measure of effect, meaning that there is enough consistent data with sufficient precision and few biases to warrant this judgment
    - Moderate quality means that further research is likely to have an important impact on confidence in the size of the effect and may change the estimate of effect
    - Low quality evidence means that further research is very likely to have an important impact on the estimate of effect and is likely to change that estimate
    - Very low quality evidence means that there is great uncertainty about the estimate of the effect
    - No evidence means that no RCTs were identified

Results:
- 27 RCTs, analyzing 1522 patients, were selected representing manipulation or mobilization as single-modal interventions
- All trials were small; no study had more than 70 patients
- 16 trials studied the effects of manipulation alone of the cervical region; 4 had a low risk and 12 a high risk of bias
  - There was moderate quality evidence from 2 trials with 369 patients (1 with low and one with high risk of bias) that manipulation produces similar changes in pain, function, and patient satisfaction when compared to mobilization for subacute or chronic neck pain at short and intermediate follow-up
  - There was low quality evidence from 3 trials with 130 patients (2 with high and 1 with low risk of bias) that manipulation alone versus a control (wait list, sham treatment, or muscle relaxant) may provide immediate and short-term pain relief after 1-4 sessions for acute or chronic neck pain
  - There was very low quality evidence that no manipulation technique is superior to any other for subacute neck pain
  - There was very low very low quality evidence that manipulation was equivalent to some medications (muscle relaxant, NSAID),
acupuncture, and soft-tissue treatment such as massage and trigger-point treatment for subacute and chronic neck pain

- There was very low quality evidence that manipulation may be superior to TENS for cervicogenic headache
  - 6 trials studied the effect of manipulation of the thoracic region alone; 1 had low and 5 had a high risk of bias
    - There was low quality evidence from the 1 study with low risk of bias favoring a single session of thoracic manipulation compared to placebo for chronic neck pain
    - Other comparisons were based on studies with high risk of bias regarding the effect of thoracic manipulation on neck pain
  - 8 trials studied the effect of mobilization alone of the cervical region; 5 had a low risk of bias and 3 had a high risk of bias
    - There was moderate to low quality evidence showing no difference between mobilization and manipulation for pain, function, and patient satisfaction for subacute and chronic neck pain
    - No other comparisons of mobilization rose to the level of moderate quality evidence, although one trial with a high risk of bias reported that anterior-posterior mobilization was more immediately effective than transverse oscillatory and rotational mobilization for neck pain
  - Only 8 trials mentioned side effects; 3 of these reported no side effects, and 5 reported benign and transient side effects in the treatment group; occurrence of serious effects of stroke could not be established
  - None of the trials measured the costs of care

Authors’ conclusions:
- The quality of reporting of clinical trials for manipulation and mobilization has not improved in recent years
- The available evidence suggests some immediate or short-term pain relief with cervical manipulation and mobilization alone, but there is no evidence for long-term relief
- For whiplash, there is a dearth of evidence for manipulation and mobilization
- The optimal “dosage” of treatment, either in frequency, number of sessions, or duration of treatment, remains unclear
- Cervical manipulation and mobilization produce similar results for pain, function, and patient satisfaction
- Thoracic manipulation may improve pain and function for chronic neck pain
- Anterior-posterior mobilization may be superior to transverse rotational mobilization for pain and function

Comments:
- For thoracic manipulation, only one study (Cleland et al 2005) was rated as having a low risk of bias; one study (Gonzalez-Iglesias 2009) was rated as having a high risk of bias, but could have been rated as having a low risk of bias if given credit for patient blinding
- The issue of patient blinding for Gonzalez-Iglesias 2009 is open to discussion; the study did not inform the patients that thoracic thrust manipulation was the intervention being evaluated by the randomized trial, and withholding this information could control bias that would arise if the patients knew why the study was being done
- The credibility of thoracic thrust manipulation could be greater than would be indicated by a single trial of low bias if Gonzalez-Iglesias 2009 is rated as having a low risk of bias
- The superiority of anterior-posterior mobilization over transverse mobilization, though in the authors’ conclusions, does not appear to rise to the level of adequate evidence, since it is based on a single study with high risk of bias
- These judgment matters aside, the overall state of the evidence appears to be of low quality, based on the size of trials and the difficulty of controlling bias
- The lack of follow-up beyond the immediate and long term also places great constraints on the suitability of the interventions for neck pain in patient populations in any setting
- The literature search and assessment, together with the integration of the studies into the GRADE system, were of high quality
- Small randomized trials such as those included in this meta-analysis are poorly equipped to detect potentially serious adverse effects such as vertebral artery dissection, and no conclusions can be drawn regarding the safety of cervical manipulation

Assessment: High quality meta-analysis with limited support for manipulation and mobilization:
- Some evidence that manipulation provides immediate and short-term relief for acute and chronic neck pain
- Some evidence that manipulation and mobilization produce comparable relief of subacute and chronic neck pain in the short and intermediate term
- Some evidence that thoracic thrust manipulation may improve pain and function for mechanical neck pain