Review article

Predictive factors for reporting adverse events following spinal manipulation in randomized clinical trials — secondary analysis of a systematic review

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ABSTRACT

While spinal manipulative therapy (SMT) is recommended for the treatment of spinal disorders, concerns exist about adverse events associated with the intervention. Adequate reporting of adverse events in clinical trials would allow for more accurate estimations of incidence statistics through meta-analysis. However, it is not currently known if there are factors influencing adverse events reporting following SMT in randomized clinical trials (RCTs). Thus our objective was to investigate predictive factors for the reporting of adverse events in published RCTs involving SMT. The Physiotherapy Evidence Database (PEDro) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for RCTs involving SMT. Domains of interest included: sample size; publication date relative to the 2010 CONSORT statement; risk of bias; the region treated; and number of intervention sessions. 7398 records were identified, of which 368 articles were eligible for inclusion. A total of 140 (38.0%) articles reported on adverse events. Articles were more likely to report on adverse events if they possessed larger sample sizes, were published after the 2010 CONSORT statement, had a low risk of bias and involved multiple intervention sessions. The region treated was not a significant predictor for reporting on adverse events. Predictors for reporting on adverse events included larger sample size, publication after the 2010 CONSORT statement, low risk of bias and trials involving multiple intervention sessions. We recommend that researchers focus on developing robust methodologies and participant follow-up regimens for RCTs involving SMT.

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1. Introduction

Manual therapy is a commonly used intervention to treat musculoskeletal disorders of the spine (Bronfort et al., 2010; Clar et al., 2014). It includes spinal manipulative therapy (SMT) directed at a vertebral joint with the intention of moving the joint past its physiological range of motion without exceeding the anatomical limit (Bergmann and Peterson, 2011; Herzog, 2010). While clinical practice guidelines recommend the use of SMT in the treatment of neck and back disorders (Airaksinen et al., 2006; Koes et al., 2010; The Canadian Chiropractic A et al., 2005), concern still exists about adverse events associated with this type of intervention, particularly when applied to the cervical spine (Ernst, 2007; Carnes et al., 2010a; Gouveia et al., 2009; Rubinstein et al., 2005; Carlesso et al., 2010).

Well-designed randomized clinical trials (RCTs) provide the most reliable results when investigating the efficacy of healthcare interventions (Cartwright, 2007; Sibbald and Roland, 1998). However, poorly designed RCTs tend to exaggerate treatment effects, which, when combined with inadequate reporting, may misinform the decision making process at all levels of health care, and negatively influence the development of clinical practice guidelines and health care policy (Moher et al., 1998, 2010).

In an effort to reduce the reporting of exaggerated treatment effects and bias, the Consolidated Standards of Reporting Trials (CONSORT) statement was first published in 1996 and subsequently updated in 2001 and 2010 respectively (Begg et al., 1996; Altman et al., 2001; Schulz et al., 2010). In 2004, an extension to the statement, specifically addressing the reporting of adverse events,

was published. This extension discussed the inadequacy of current reporting and provided 10 recommendations which were later adopted in the 2010 version of the statement (Ioannidis et al., 2004). Recent reviews investigating the overall quality (Karpouzis et al., 2016) and adequacy of adverse events reporting (Gorrell et al., 2016) in RCTs involving SMT have highlighted that the current level is inadequate and unacceptable. Trial sample size was recently reported as a factor influencing the overall quality of reporting in RCTs involving chiropractic (Karpouzis et al., 2016), however, factors influencing the reporting of adverse events in published RCTs involving SMT have not been previously reported. The objective of this secondary analysis is to investigate possible predictive factors for the reporting of adverse events in published RCTs involving SMT.

2. Methods

This is a secondary analysis of a systematic literature review (Gorrell et al., 2016) which was written adhering to the PRISMA guidelines (Higgins et al., 2011).

2.1. Eligibility criteria

Spinal manipulative therapy (SMT) was defined as manual therapy involving a high-velocity, low amplitude manipulation directed at a vertebral joint with the intention of moving the joint past its physiological range of motion without exceeding the anatomical limit (Bergmann and Peterson, 2011; Herzog, 2010). Spinal manipulation delivered using mechanical instruments and/or drop-table mechanisms were included in this review as they have been classified as high-velocity, low amplitude procedures in the literature (Bergmann and Peterson, 2011; Ostenbauer et al., 1992; Pickar, 2002). Randomized clinical trials that reported original data from SMT, either as the sole intervention or as part of a multi-modal intervention, delivered by a regulated manual therapy practitioner were eligible for inclusion in this review. We excluded: manuscripts reporting all other trial designs; commentaries; editorials; reviews; trial protocols; conference proceedings; manuscripts not available in English; retracted manuscripts; secondary analyses; if the intervention was applied to a region other than the spine; if the intervention was self-administered (e.g. exercise); and if it was unclear if the SMT applied was high-velocity, low amplitude in nature.

2.2. Search strategy

PEDro (Physiotherapy Evidence Database) and Cochrane CENTRAL (Central Register of Controlled Trials) were electronically searched from inception to February 2016. The following terms and derivatives were adapted for each search engine: *(spine, spinal, manipulation, musculoskeletal, chiropractic, osteopathy)* AND *(clinical trial)*. See Appendix 1 for the complete search strategy for the Cochrane CENTRAL database.

2.3. Study selection process

Records retrieved from the electronic searches were exported to the EndNote X7® program. Duplicate records were removed prior to titles and abstracts being screened. Two authors (LG and BB) independently conducted the study selection process. Full-text versions of the remaining potentially eligible articles were retrieved and subsequently subjected to the eligibility criteria. Any disagreements were resolved by consensus; if consensus could not be reached, disagreements were resolved using a third author (RE).

2.4. Data extraction

Articles used in this secondary analysis had previously been classified as either reporting or not reporting adverse events. The determination of whether to classify an event as 'adverse' was based on the description of the event within the manuscript and included terms such as 'adverse events', 'side effects', 'adverse effects' and 'harms' (Gorrell et al., 2016). Data extraction for this analysis was performed independently by two authors (LG and BB) using the previously established reference sample (Gorrell et al., 2016). Any disagreements were resolved by consensus; if consensus could not be reached, disagreements were resolved using a third author (RE). We extracted data for six predictive variables of interest that were chosen *a priori*. The authors discussed the selection of predictive variables in several consensus meetings. Two important selection considerations were: availability of data (i.e. that the variable could be consistently extracted from the published articles) and statistical power (i.e. to limit the number of variables and collapse categories while still being able to perform meaningful analyses). Specific data included: sample size; publication date; risk of bias; the region treated, classified as either 'back' or 'neck'; and number of intervention sessions. Publication date was dichotomized into before or after the publication of the 2010 CONSORT statement. Region treated was dichotomized into treatment of the neck (cervical spine only) or back (other regions of the spine, in addition to or in place of treatment of the neck). Number of intervention sessions was dichotomized into single intervention session or multiple intervention sessions. Methodological quality of the trial was assessed using the Cochrane risk of bias (ROB) assessment tool (Moher et al., 2009) and dichotomized into high risk or low risk. The ROB assessment was conducted independently by two authors (LG and RE). Any disagreements were resolved by consensus; if consensus could not be reached, disagreements were resolved using a third author (BB).

2.5. Data analysis

All statistical analyses were performed using the statistical computing software R version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were produced for both the continuous and categorical variables of interest. Any observed differences between the articles that reported adverse events and those that did not were evaluated i): univariately, with t-tests for the continuous variables and Pearson's chi squared test with Yates' continuity correction for categorical variables; and ii) multivariately, with binomial logistic regression. All univariate and multivariate results were reported with 95% confidence intervals and test statistics with corresponding p-values. The following assumptions for statistical tests were checked: *t*-test, independence of observations, normal distribution of the dependent variable (assessed using Shapiro-Wilk test), and equal variance across groups (assessed using Levene's test); chi-square test, independence of observations, and sufficient sample size and expected cell counts (assessed by evaluating contingency table cell counts); binomial logistic regression, independence of observations, and no multicollinearity (assessed using generalised variable inflation factor).

3. Results

There were 7398 records initially identified by the electronic searches. A total of 6382 unique records remained after the removal of duplicates. After screening titles and abstracts, a total of 710 potentially eligible articles remained, of which 368 articles fulfilled the eligibility criteria. See Fig. 1 for a detailed description of the