COMPARATIVE CLINICAL EFFECTIVENESS OF MANAGEMENT STRATEGIES FOR SCIATICA: SYSTEMATIC REVIEW AND NETWORK META-ANALYSES

Lewis R, Williams NH, Sutton AJ, Burton K, Din N, Matar HE, Hendry M, Phillips CJ, Nafees S, Fitzsimmons D, Rickard I, Wilkinson C. Comparative Clinical Effectiveness of Management Strategies for Sciatica: Systematic Review and Network Meta-Analyses, The Spine Journal 2013, doi: 10.1016/j.spinee.2013.08.049

ABSTRACT

Background

There are numerous treatment approaches for sciatica. Previous systematic reviews have not compared all these strategies together.

Purpose

To compare the clinical effectiveness of different treatment strategies for sciatica simultaneously.

Study design

Systematic review and network meta-analysis.

Methods:

We searched 28 electronic databases and online trial registries, along with bibliographies of previous reviews, for comparative studies evaluating any intervention to treat sciatica in adults, with outcome data on global effect or pain intensity. Network meta-analysis methods were used to simultaneously compare all treatment strategies and allow indirect comparisons of treatments between studies. The study was funded by the UK National Institute for Health Research (NIHR) HTA programme; there are no potential conflict of interests.

Results

Of 122 relevant studies, 90 were randomised controlled trials (RCTs) or quasi-RCTs. Interventions were grouped into 21 treatment strategies. Internal and external validity of included studies was very low. For overall recovery as the outcome, compared with inactive control or conventional care, there was a statistically significant improvement following disc surgery, epidural injections, non-opioid analgesia, manipulation, and acupuncture. Traction, percutaneous discectomy and exercise therapy were significantly inferior to epidural injections or surgery. For pain reduction

as the outcome, epidural injections and biological agents were significantly better than inactive control, but similar findings for disc surgery were not statistically significant. Biological agents were significantly better for pain reduction than bed rest, non-opioids, and opioids, ~~or radiofrequency treatment~~. Opioids, education/advice alone, bed rest, and percutaneous discectomy ~~and radiofrequency treatment~~ were inferior to most other treatment strategies; although these findings represented large effects, they were statistically equivocal.

Conclusions

For the first time many different treatment strategies for sciatica have been compared in the same systematic review and meta-analysis. This approach has provided new data to assist shared decision-making. The findings support the effectiveness of non-opioid medication, epidural injections and disc surgery. They also suggest that spinal manipulation, acupuncture, and experimental treatments such as anti-inflammatory biological agents, may be considered. The findings do not support the effectiveness of opioid analgesia, bed rest, exercise therapy, education/advice (when used alone), percutaneous discectomy or traction. The issue of how best to estimate the effectiveness of treatment approaches according to their order within a sequential treatment pathway remains an important challenge.

KEY WORDS

Systematic Review; Sciatica; Intervertebral disc herniation; network meta-analyses; indirect treatment comparisons; Clinical Effectiveness;treatment strategies

INTRODUCTION

Sciatica is the term used for the syndrome characterised by radicular leg pain, with or without sensory deficits, radiating along the distribution of the sciatic nerve.[1-3] In about 90% of cases, it is caused by an intervertebral disc herniation resulting in nerve root irritation.[4-6] It is a common reason for seeking medical advice,[7,8] and has considerable economic consequence in terms of healthcare resources and lost productivity.[7] The diagnosis and management of sciatica varies considerably within and between countries,[4] which may reflect treatment availability, clinician preference and socio-economic variables rather than evidence-based practice.

Previous systematic reviews (including meta-analyses) have evaluated the effectiveness of various individual treatment approaches for sciatica, including conservative treatments,[9-12] epidural steroid injections,[9,11,13,14] and surgical procedures.[15] However, numerous treatments have not been directly compared. Furthermore, in order to choose the optimal treatment(s), it would be more helpful if all candidate treatments could be compared in the same analysis, as opposed to using a series of simple but inefficient standard pairwise meta-analyses comparing only two treatments at a time. It has been acknowledged that there is difficulty in interpreting the findings of multiple comparisons with low power, due to the small number of participants or events, which are inclined to result in statistically insignificant findings.[16,17]

A network meta-analysis,[18] by contrast, enables the simultaneous comparison of more than two treatment approaches, whilst combining data derived from both direct within-study comparisons between two treatment strategies (e.g A vs B) and comparisons constructed from two studies that have one treatment in common (e.g. A vs B, B vs C).[17] This type of analysis can only be applied to connected networks of randomised controlled trials (RCTs),[19] but preserves the within-trial randomised comparison of each study[19] and allows information on treatment strategies to be "borrowed" from other studies within the network, thereby increasing the total sample size.[20,21] Network meta-analysis conducted using Bayesian methods[22-24] also allows the treatment strategies to be ranked in terms of clinical effectiveness with an estimate of the probability that each strategy is 'best'.[25]

Our primary aims were to simultaneously compare the clinical effectiveness of different treatment strategies for sciatica using network meta-analyses, in order to identify the best treatment and to provide estimates for all possible pairwise comparisons, based on both direct and indirect evidence. Our secondary aims were

to demonstrate the feasibility of using network meta-analyses as a rational basis for clinical decision making when a number of treatment options are available and where a series of conventional systematic reviews have failed to help with real-world treatment decisions. The analyses presented in this paper represent a refinement of initial network meta-analyses conducted as part of a broader Health Technology Assessment (HTA) evaluating the clinical and cost effectiveness of treatments for sciatica. A full account of the study methods and literature search are presented in the HTA monograph (which also includes the protocol).[16]

METHODS

Search strategy

Included studies were identified via an extensive literature search described in full, including the search strategy, in the HTA monograph.[16] The search incorporated 28 electronic databases and trial registries including MEDLINE, EMBASE, and AMED. Databases were searched from inception until December 2009 without language restriction. The reference lists of previous systematic reviews and included studies were also scanned for further references.

Study selection and data extraction

This review included any comparative study (experimental or observational) with adults who had sciatica diagnosed clinically, or where clinical imaging confirmed lumbar disc prolapse consistent with the clinical findings. The essential clinical criterion was radicular leg pain worse than back pain.[16] Studies of sciatica caused by conditions other than a prolapsed intervertebral disc were included if it was documented that radicular leg pain was worse than back pain. If imaging was used, it had to demonstrate evidence of nerve root compromise. Studies that included participants with non-specific low back pain were only included if the findings for patients with sciatica were reported separately. Any type of intervention to treat

sciatica was considered. These were categorised, for the purpose of the present analyses, into one of 21 categories (See Table 1). Interventions that included a combination of more than one treatment strategy (or mixed treatments) were excluded from the network meta-analyses due to uncertainty regarding the extent of interaction between the combined interventions. The same applied to post-surgical interventions due to surgery being included as a separate treatment category. Studies comparing interventions that were grouped under the same treatment strategy were also excluded. Three further studies evaluating experimental interventions for sciatica (common peroneal nerve block,[26] protolytic enzyme,[27] and colchicine[28]) were excluded from the analyses as these interventions did not fit the treatment categorisation. For the present network meta-analyses we concentrated on overall response and pain intensity rather than back specific function, so three studies which only reported outcome data for back specific function were excluded.[29-31]

[Table 1: Treatment categorisation]

Two reviewers screened studies for inclusion independently. Data were extracted by one reviewer and checked by a second using the original paper, whilst quality assessment was done by two reviewers independently. Any disagreements were resolved by discussion. The quality of both trials and observational studies was assessed using the same checklist, which was based on one used by the Back Review Group of the Cochrane Collaboration for RCTs[32] and another recommended by the Guidelines for Systematic Reviews in Health Promotion and Public Health Taskforce[33] (developed by the Effective Public Health Practice Project, Canada[34]). The criteria covered external validity, selection bias and confounding, detection bias, performance bias, and attrition bias. Studies were coded as strong, moderate or weak for each domain, estimating the risk of bias.

Outcome measures

Overall response or global effect was analysed as a binary outcome (treatment success vs failure) and synthesised using odds ratios (ORs). Where studies reported overall response in terms of both overall improvement and improvement in leg pain, the data on overall improvement were used. For studies that reported both physician and patient perceived global effect, the data for patients' perceived effect were used.

Pain intensity (on a scale of 0-100) was analysed as a continuous outcome measure using weighted mean difference (WMD). We only included pain assessment from one location from each study using the preference hierarchy of leg pain then overall pain. Where feasible, missing data were estimated from the published data, using standard methods, such as standard deviations (SDs) derived from standard errors (SEs).[35] Where mean values were unavailable but the medians were reported, these were used instead. If SDs for baseline values were available these were substituted for missing SDs. For studies that did not report sufficient data to derive the SDs, they were imputed using the weighted mean,[36] which was calculated separately for each intervention category.

Statistical analysis

The network meta-analyses were based on a single time point, using the findings from individual studies closest to six months follow-up. Sensitivity analyses were conducted to assess the impact of excluding non-randomised studies (observational studies and non-RCTs).

The network meta-analyses were conducted using a hierarchical random-effects model[18] within the Bayesian framework. Bayesian methods are based on the idea that unknown quantities, such as population means or proportions, have probability

distributions.[23] You start with a distribution that is based on prior knowledge or subjective belief about the population and then update this using data from your included studies. However, using non-informative priors (such as, a normal distribution with a large variance) means that the results are based predominantly on the data from the included studies, and as such will mirror those obtained using frequentist or classical meta-analysis methods. Bayesian methods are implemented using model-based simulations, which means that they can be used to perform complex analyses that incorporate multiple data sources and allow for various parameter uncertainties within a single coherent model, which is why we chose to use these methods.

Our network meta-analyses were conducted using WinBUGS1.4.3 software,[37] which uses Markov chain Monte Carlo (MCMC) simulation methods to run thousands of simulated iterations based on the data and description of the proposed distributions for relevant parameters. The iterative simulations area generally started at multiple points in order to ensure the samples are drawn from the whole sampling frame. The first 50,000 iterations (or burn-in) were discarded, and the results are based on a further sample of at least 50,000 simulations, ensuring that the multiple simulation strings have converged and distributions were informed by later simulations. Numerical methods such as the Brooks-Gelman-Rubin statistic[37] and the inspection of the auto-correlation and history plots, which are routine assessments made when using MCMC methods, were used to check that convergence had occurred. The model fit was checked by the global goodness of fit statistic, residual deviance. If the model is an adequate fit, it is expected that the residual deviance should be roughly equal to the number of data points.[19] Non-informative priors were used for normal distributions for means, and uniform distributions for standard deviations. The treatment strategy ‘inactive control’ was used as the reference treatment. This included interventions that represent the non (active) treatment of sciatica, such as

no treatment, sham treatment, or placebo (two studies used active placebo). The WinBUGS codes (or models) that we used are presented in Supplementary Material (Web Appendix A). The robustness of the network meta-analyses were also evaluated by comparing the findings (where head to head studies were available) with those of standard 'direct' pairwise meta-analyses[16] conducted using a random-effects model[38] based on frequentist methods[22-24] in Stata 10.

The assumptions of a random-effects network meta-analysis are that (1) the treatment effects are additive (i.e. the relative effect of treatment A vs C can be estimated from the effect of A vs B and B vs C);[19,39,40] (2) study-specific treatment effects are drawn from a common distribution (exchangeable);[19,41] and (3) this common distribution or heterogeneity is constant between the different comparisons.[19,41] We evaluated heterogeneity between studies, defined as the variability of the results across studies within each treatment comparison over and above chance,[42] by examining the findings of standard pairwise meta-analyses using visual inspection of the forest plots, as well as Chi^2 statistic to test for the I^2 statistic to quantify statistical heterogeneity.[43,44]

RESULTS

Included studies

As seen in Figure 1, 122 studies were included in the revised network meta-analyses[45-165] (one publication included two studies[119]), 86 were RCTs[48,49,51,52,54,56-62,64,66,67,69-71,73-76,78-83,85,87-90,93,95-97,99-101,103,105-107,110,111,114-124,126-128,130,132-141,143-145,149-155,158,159,161,164] and four Q-RCTs.[46,91,104,109] The network meta-analysis of global effect included 95 studies (68 RCTs/Q-RCTs) and pain intensity 53 studies (46 RCTs/Q-RCTs). A description of the interventions, populations, study design, and outcome

data for the pairwise studies are presented in Supplementary Material (Web Appendix B).

[Figure 1: flow diagram showing the number of references identified, publications retrieved for assessment, and studies included in the review]

Eleven (9%) studies had a strong overall quality rating[58,79,97,99,116,128,132,140,152,155,161] and eight (7%) had a strong overall external validity rating;[97,100,116,121,128,140,153,155] five (4%) of which had a strong rating for both.[97,116,128,140,155] Only 26 (21%) studies used both adequate randomisation and adequate or partially adequate (using sealed envelopes, n=16) allocation concealment.

The proportion of studies that limited inclusion to patients with acute sciatica (duration of symptoms <3 months) was much higher in conservative treatments, such as traction (71%), bed rest (80%), and non-opioid medication (53%), than more invasive treatments (such as disc surgery 8%, chemonucleolysis 3%, and epidural 5%). However, most studies did not report the duration of sciatica, or included patients with acute and chronic sciatica. The presence of disc herniation was also confirmed by imaging in a high proportion of studies evaluating invasive treatments such as percutaneous discectomy (100%), disc surgery (86%) and chemonucleolysis (84%). Previous treatment was poorly reported in many studies, but the proportion of studies that reported patients who had received previous treatment was higher for invasive treatments such as disc surgery (70%), percutaneous discectomy (100%), and chemonucleolysis (88%), than for conservative treatments such as non-opioids (20%), traction (29%), and acupuncture (33%). The mean pain score (where reported), at baseline for each treatment strategy were fairly similar (ranging from 59 to 69) with the exception of biological agents (78).

Figure 2 shows the network of treatment comparisons for the network meta-analysis of global effect and Figure 3 shows the same for the analysis of pain intensity.

[Figure 2: Network of treatment strategies for sciatica for comparative studies reporting global effect]

[Figure 3: Network of treatment strategies for sciatica for comparative studies reporting pain intensity]

Summary effect estimates for the comparison of each intervention strategy with inactive control are presented in Figures 4-5. The corresponding confidence intervals (CIs) provide an indication of the uncertainty surrounding the effect sizes, which needs to be taken into account when interpreting the data (especially the probability of being best). The probabilities for each treatment strategy being best (or most effective) are presented in Supplementary Material (Web Appendix C). The network meta-analyses also provide a full set of comparisons for all treatment strategies, the findings of which are presented in Tables 2-3. The summary effect sizes derived from the network meta-analyses can be directly compared with the summaries of pairwise meta-analyses (derived using Stata 10), which are presented in the same matrices (top right hand corner); statistically significant findings are indicated by shading. The results of sensitivity analyses restricted to RCTs and Q-RCTs are presented in Supplementary Material (Web Appendix C-D).

[Figure 4: Plot of the odds ratios (ORs) of global effect for different treatment strategies compared with inactive control from the network meta-analysis]

[Figure 5: Plot of the weighted mean difference for pain intensity for different treatment strategies compared with inactive control from the network meta-analysis]

[Table 2: Results (odds ratios, with 95% confidence intervals/credible intervals) of the network meta-analysis for global effect]

[Table 3: Results (weighted mean difference, with 95% confidence intervals/credible intervals) of the network meta-analysis for pain intensity]

Overall response

In terms of overall response or global effect, the following treatment comparisons with inactive control (A) or conventional care (B) were statistically significant at the 5% level: disc surgery (C), epidural injections (D), non-opioids (F), intra-operative interventions (G), which includes interventions such as barrier membranes and steroids used during the surgical procedure, spinal manipulation (I), acupuncture (J), and chemonucleolysis (E). Intradiscal injections (S) were found to be statistically significantly worse than disc surgery (C), epidural injections (D), non-opioids (F), intra-operative interventions (G), manipulation (I), and acupuncture (J). Percutaneous discectomy (Q) was found to be inferior to disc surgery (C), epidural injections (D), and intra-operative interventions (G). Traction (H) and exercise therapy (K) were also found to be inferior to epidural injections and intra-operative interventions. Radio frequency treatment (U) was statistically significantly inferior to disc surgery (C), epidural injections (D), intra-operative interventions (G), and acupuncture (J). Finally, chemonucleolysis (E) was statistically significantly less effective than epidural injections, disc surgery, and intra-operative interventions. The largest treatment effects for the comparison with inactive control were for biological agents and acupuncture, which also had the highest probability of being best (0.57 and 0.26

respectively). The comparison of biological agents with the following treatments also showed large effect estimates (OR >10), but these were not statistically significant: chemonucleolysis (E), traction (H), exercise therapy (K), passive physical therapy (such as ultrasound and transcutaneous electrical nerve stimulation) (L), bed rest (N), opioid medication (O), percutaneous discectomy (Q), intradiscal injections (S), and radio frequency treatment (U), all of which were associated with very wide confidence intervals. This reflects the limited evidence available for biological agents, which included a small placebo controlled RCT (n=24) that reported a large effect estimate in favour of biological agents (OR 10.0; 95% CI: 0.65, 166.67. see Supplementary Material Table C1).

The results of the sensitivity analyses excluding observational studies and non-RCTs showed broad agreement with the main analyses. For global effect, the most notable discrepancies occurred with biological agents compared with chemonucleolysis, conventional, and care exercise therapy. A more detailed narrative of the differences between the analyses with and without the non-randomised studies is presented in the Supplementary Material (Web Appendix D)

Pain intensity

In terms of pain intensity, the only treatment comparisons with inactive control that were statistically significant were epidural injections (D) and biological agents (M). Biological agents, which had the highest probability of being best (0.33), were also found to be statistically significantly better at reducing pain than non-opioids (F), bed rest (N), opioids (O) and radio frequency treatment (U); these findings were all associated with wide credible intervals. When considering the magnitude of effect, bed rest (N), education/advice alone (P), percutaneous discectomy (Q), and radiofrequency treatment (U) tended to fare worse when compared with most treatment strategies, with findings showing a non-statistically significant difference of

more than 25 points. Acupuncture (J), had the second highest probability of being best (0.19) and resulted in reductions of pain intensity of more than 25 points compared with bed rest, opioids, education/advice alone, percutaneous discectomy and radio frequency treatment, none of which were statistically significant and all had wide credible intervals.

For pain intensity the most notable discrepancies between the network meta-analysis with and without observational studies and non-RCTs only occurred with biological agents (vs inactive control, conventional care, disc surgery, non-opioids, intra-operative interventions, acupuncture, exercise therapy, opioids, and neuropathic painmodulators). Biological agents no longer had the highest probability of being best (0.03; see Supplementary material Table C4). These discrepancies are likely to be due to the small number of included studies with a limited number of participants evaluating biological agents (2 RCTs n=131; 1 non-randomised RCT n=72; and 1 historical cohort study n=10).

Between study heterogeneity, model fit and comparison with standard pairwise meta-analyses

Based on the Gelman-Rubin statistic, convergence occurred at around 6-8000 iterations for both outcome measures (global effect, pain intensity). The auto-correlation and history plots also showed good convergence. The goodness of fit of the models to the data, measured by the residual deviance, was found to be good for all three outcomes (Supplementary Material, Web Appendix E).

The results of the evaluation of between-study heterogeneity showed a moderate to high level[16] of statistical heterogeneity for many of the pairwise comparisons, as well as across all studies as a whole. The heterogeneity was greater for the analysis of

pain intensity than global effect, with an I^2 statistic of less than 75% (i.e. moderate or less) for all but one pairwise comparison (epidural injections vs conventional care). The observed values for I^2 are presented in Figure 1. Heterogeneity did not improve when non-randomised studies were removed.

The comparison of the results from the network meta-analyses with that of the conventional pairwise meta-analyses showed broad agreement with slightly more discrepancies for the analyses of pain intensity. These discrepancies were greatest for comparisons that had very little direct evidence, such as biological agents.

DISCUSSION

This is the first systematic review that has included all treatment strategies for sciatica in the same analysis using a network meta-analysis method that includes indirect comparisons. The advantages of such analyses are that they can simultaneously compare more than two treatments in the same coherent analysis; provide relative effect estimates for all treatment comparisons, even those that have not been directly compared in head to head trials; enable the estimation of the probability that each treatment is best; and reduce the uncertainty in the treatment effect estimates.

Summary of results

In terms of overall response or global effect, there was a statistically significant improvement following disc surgery, epidural injections, non-opioid medication, intra-operative interventions, manipulation, and acupuncture when compared with inactive control or conventional care. Epidural injections, disc surgery, and intra-operative interventions were also statistically significantly better than percutaneous

discectomy, chemonucleolysis, intradiscal injections, and radiofrequencly treatment., with epidural injections, and intra-operative interventions also statistically significantly better than both traction, and exercise therapy. While biological agents and acupuncture had the highest probability of being best and had the largest effect estimates when compared with inactive control, these findings were associated with very wide credible intervals, reflecting the lack of information on these effect estimates.

In terms of pain intensity, there was a statistically significant reduction in pain following epidural injections and biological agents compared with inactive control, but there was no significant difference between disc surgery and inactive control. Biological agents had the highest probability of being best, and were also statistically significantly better than non-opioid medication, opioid medication, bed rest, and radio frequency treatment. However, when the analysis was restricted to RCTs, biological agents no longer had the highest probability of being best and were not found to be statistically better than any other treatments. When considering the magnitude of effect, bed rest, education/advice alone, percutaneous discectomy, and radiofrequencly treatment were considerably inferior when compared with most treatment strategies, but these findings were not statistically significant and were associated with wide credible intervals.

Overall, the results of the sensitivity analyses excluding non-randomised studies showed broad agreement with the main analyses, with the findings generally becoming non-statistically significant due to broader credible intervals for the analyses restricted to RCTs and Q-RCTs. The most notable discrepancies occurred with treatment strategies that were associated with a small number of included studies such as those reporting treatment with biological agents.

Findings of previous reviews

Previous reviews of non-surgical treatments have either found no evidence of effectiveness,[9,10] conflicting evidence,[11,12] or have reached different conclusions concerning the effectiveness of epidural steroid injections.[9,11,13,14,166,167] A Cochrane systematic review of surgical interventions did not combine the results of four RCTs comparing discectomy with non-surgical treatment due to heterogeneity, and concluded that the results showed a temporary benefit of disc surgery at one year follow-up.[15] In that review the effectiveness of discectomy was justified by using informal indirect comparison of chemonucleolysis with placebo, and chemonucleolysis with disc surgery; chemonucleolysis was more effective than placebo and discectomy more effective than chemonucleolysis, therefore disc surgery was superior to placebo. Using our network meta-analyses, it was possible to make a more robust statement on disc surgery compared with placebo: disc surgery was statistically significantly better than placebo in terms of global effect but not for pain intensity.

Strengths and weaknesses

One of the main strengths of our network meta-analyses is the wide range of treatment strategies used to treat sciatica that were not only considered in the same review, but compared simultaneously in the same analysis. Another strength is that they were based on a systematic and comprehensive search of the literature up (until December 2009) that covered any therapeutic intervention for sciatica. Although we acknowledge that these searches are not current, and as such, more recent relevant data is likely to have been excluded.

The RCT is widely regarded as the design of choice when assessing the effectiveness of health care interventions[168] and we acknowledge the controversy

over the inclusion of non-randomised evidence. Non-randomised studies were included in the search because some treatment approaches may not have been evaluated by RCTs, and also to increase the precision of the findings for interventions evaluated by a limited number of studies. Observational studies can have better external validity than RCTs[169,170] and provide more generalisable findings. However, observational studies are likely to be affected by selection bias and confounding, and may therefore yield estimates of association that deviate from the true underlying relationship beyond the play of chance.[171] As it happens, most of the RCTs did not report the method of generating the randomisation sequence or allocation concealment, which means that selection bias or confounding might still be present. Excluding the non-randomised studies in a sensitivity analysis did not affect the structure of the network and the overall findings of both series of network meta-analyses were similar, although less precise for the analyses of RCTs.

Network meta-analysis methods enabled us to go beyond the pairwise comparisons reported in previous systematic reviews. They allowed us to simultaneously compare all the available treatment strategies for sciatica and provided estimates of relative treatment effects for all conceivable comparisons, even those where there was no direct evidence available. However, the small number of relevant studies for some comparisons, statistical heterogeneity (within pairwise comparisons), and potential inconsistency (between pairwise comparisons) within the networks means that the encouraging results for interventions such as biological agents should be interpreted with caution.

In order to answer the question of which is the optimum treatment for sciatica and provide generalisable findings, we were interested in the average treatment effect of each treatment approach (to represent the diversity used in clinical practice). We therefore pooled clinically heterogeneous studies. We used a random-effects model

to pool the data, which is based on the assumption that different studies assessed different, yet related, treatment effects. However, included studies also varied in study design and risk of bias (methodological diversity). There was considerable (I^2 ≥75%)[43] statistically significant between-study heterogeneity present for a number of comparisons within the pairwise meta-analyses, especially in the analyses of pain intensity, and it was not possible to ascertain how much was due to clinical or methodological diversity. This needs to be taken into consideration in future work.

The network meta-analyses relied on the key assumption that the relative treatment effect of one treatment versus another is the same across the entire set of studies.[18,41] The use of random-effects models meant that it was assumed that the common distribution of effects was the same across all sets of studies. A further assumption made in the analyses was that the relative efficacy of different treatments is the same at different stages in the care pathway. Pragmatically, sciatica is often treated with a stepped care approach starting with conservative treatments, such as non-opioid medication, progressing if necessary to more invasive treatments such as epidural injections or surgery. This means that the population of patients treated with conservative treatments was likely to differ from those treated with invasive treatments, resulting in confounding and inconsistency within the network. Although descriptive characteristics were generally poorly reported by included studies, there was a trend for studies evaluating invasive treatments to report a history of previous treatments and include patients with a diagnosis confirmed by imaging, and for studies of conservative treatments to limit inclusion to patients with acute sciatica. Due to the breadth of the review and the novel and speculative use of network meta-analysis methods, we have not yet incorporated stepped care approaches in the network meta-analyses. The optimum sequence of treatment modalities and what sequence is best for which patients is therefore not yet known and awaits further analysis.

The network meta-analyses were based on a single time point, outcome data closest to six months, which may be considered as a limitation of the analyses. The HTA monograph[16] included an assessment of each treatment strategy at short (≤ 6 weeks), medium (> 6weeks to ≤ 6 months) and long (> 6 months) term follow-up, but this evaluation was based on multiple pairwise analyses, with each analysis needing to be interpreted independently. Further research is needed to incorporate multiple time points within the network meta-analyses in order to incorporate data at different follow-up periods.

For the pain intensity outcome, where the SDs were missing (and could not be estimated from the published data) these were imputed using the weighted mean SD[36,172] for each treatment strategy (11 studies). This is based on the assumption that the variance is similar between studies and the data are not skewed.[173] We also used medians to represent the mean for two studies. We considered that it was better to use these methods in order to incorporate more of the evidence base, as ignoring the findings of these studies may induce bias in the summary effect estimate.[172] Furukawa, et al.[36] have previously shown that it is safe to borrow SDs from other studies.

There were insufficient studies to explore the presence of publication or reporting bias for most treatment comparisons. However, a funnel plot of studies comparing surgery and chemonucleolysis showed no evidence of publication bias.[16] The benefit (or effectiveness) of different treatment strategies for sciatica should be considered along with potential harms. Although the present paper does not report adverse effects, they are reported elsewhere.[16]

CONCLUSIONS

The use of network meta-analyses has enabled us to provide new information on the relative effectiveness of treatments for sciatica. This can help clinicians and patients in shared decision making, as well as providing data for healthcare policy development. The findings provide support for the effectiveness of some common therapies for sciatica such as non-opioid medication, epidural injections and disc surgery. They also suggest that less frequently used treatments such as manipulation and acupuncture, and experimental treatments such as cytokine modulating biological agents, may be considered. The findings of this review do not support the effectiveness of opioid medication, either for pain intensity or global effect. Furthermore, there is no support for the effectiveness of numerous other interventions such as bed rest, exercise therapy, percutaneous discectomy or traction. The lack of support for education/advice should not be taken to imply that patients should not be given information or advice; rather it is not an effective treatment if delivered alone.

Further research is needed to confirm or refute these findings where we found limited evidence, and to explore the impact of heterogeneity and the range of clinical questions most suited for the use of network meta-analyses. There is also scope to develop more sophisticated methods, such as building on the confidence profile method,[170] bias-adjusted results,[174] or Bayesian statistics,[169] to incorporate information relating to differences in study design or internal and external validity in the network meta-analyses, as well as data on multiple follow-up periods. The issue of how best to estimate the effectiveness of treatment approaches according to their order within a sequential treatment pathway remains an important challenge.

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