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ORIGINAL PAPER

Veterinary homeopathy: meta-analysis of randomised placebo-controlled trials

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Background: **Meta-analysis of randomised controlled trials (RCTs) of veterinary homeopathy has not previously been undertaken. For all medical conditions and species collectively, we tested the hypothesis that the outcome of homeopathic intervention (treatment and/or prophylaxis, individualised and/or non-individualised) is distinguishable from corresponding intervention using placebos.**
Methods: **All facets of the review, including literature search strategy, study eligibility, data extraction and assessment of risk of bias, were described in an earlier paper. A trial was judged to comprise reliable evidence if its risk of bias was low or was unclear in specific domains of assessment. Effect size was reported as odds ratio (OR). A trial was judged free of vested interest if it was not funded by a homeopathic pharmacy. Meta-analysis was conducted using the random-effects model, with hypothesis-driven sensitivity analysis based on risk of bias.**
Results: **Nine of 15 trials with extractable data displayed high risk of bias; low or unclear risk of bias was attributed to each of the remaining six trials, only two of which comprised reliable evidence without overt vested interest. For all *N* = 15 trials, pooled OR = 1.69 [95% confidence interval (CI), 1.12 to 2.56]; *P* = 0.01. For the *N* = 2 trials with suitably reliable evidence, pooled OR = 2.62 [95% CI, 1.13 to 6.05]; *P* = 0.02).**
Conclusions: **Meta-analysis provides some very limited evidence that clinical intervention in animals using homeopathic medicines is distinguishable from corresponding intervention using placebos. The low number and quality of the trials hinders a more decisive conclusion.** *Homeopathy* (2015) **104**, 3–8.

Keywords: Veterinary homeopathy; Randomised controlled trials; Placebo control; Systematic review; Meta-analysis

Introduction

Our group has previously identified 18 randomised placebo-controlled trials of veterinary homeopathy, published in the peer-reviewed literature and eligible for systematic review.[1,2] Risk-of-bias assessment of those trials highlighted their poor quality overall, and noted only two trials with reliable evidence and without obvious vested interest.[2] Our condition-specific analysis concluded on the findings of each of those two trials: individualised homeopathic treatment did not have a beneficial effect on bovine mastitis[3]; homeopathic *Coli* had a prophylactic effect on porcine diarrhoea.[4] Because of these mixed results from so few suitable trials, we were unable to reach generalisable conclusions about the impact of any particular homeopathic intervention in any given medical condition in animals.

The present paper therefore focuses on broader questions about the clinical impact of veterinary homeopathy. We have examined the same 18 trials,[2] across all medical conditions and species and, importantly, by style of homeopathic intervention. Accepting, *a priori*, that the material would comprise both clinical and statistical heterogeneity,[5] we have tested each of the following hypotheses:

1. **Homeopathic treatment or prophylaxis overall (all 18 trials)**: Clinical intervention in animals using homeopathic medicines is distinguishable from corresponding intervention using placebos.

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2. **Homeopathic treatment overall**: Homeopathic treatment in animals is distinguishable from the same approach using placebos.
   a. **Individualised homeopathic treatment**: Homeopathic treatment is distinguishable from the same individualised approach using placebos.
   b. **Non-individualised homeopathic treatment**: Treatment using a particular homeopathic medicine is distinguishable from the same approach using a placebo.
3. **Homeopathic prophylaxis overall**: Homeopathic prophylaxis in animals is distinguishable from the same approach using placebos.
   a. **Individualised homeopathic prophylaxis**: Homeopathic prophylaxis is distinguishable from the same individualised approach using placebos.
   b. **Non-individualised homeopathic prophylaxis**: Prophylaxis using a particular homeopathic medicine is distinguishable from the same approach using a placebo.

Methods

Matters connected with study eligibility, research design categories and the literature search strategy were described in detail in our recent papers.[1,2] Only brief descriptions are therefore given here, with additional information that is specific to the methods used for the present paper.

Identifying papers for full data extraction

Eighteen records were previously identified as satisfying the key acceptance criteria for the present study: substantive report of clinical treatment or prophylaxis trial in veterinary homeopathic medicine, randomised, controlled by placebo, and published in a peer-reviewed journal.[1] The 18 studies comprise 12 treatment trials and six prophylaxis trials.

Data extraction and management

The authors of eligible randomised controlled trial (RCT) papers were not approached for clarification on unclear or missing facets of any of their methods or results; however, original authors' cross-reference to their previously published study methods were eligible for follow-up and taken into account as appropriate. For each of two assessors (RTM and JC) working independently, relevant data were extracted and then recorded using a standardised data collection format (Microsoft *Excel*).

None of the 18 papers reported more than one trial. For a paper reporting an RCT that involved >2 groups of subjects, we focused data extraction on *only one pair of groups* as follows: treatment in preference to prophylaxis; placebo control in preference to other-than-placebo control. For studies that comprised more than one homeopathy group, the total sample size that we cite reflects the total numbers of subjects in the relevant homeopathy groups *combined*.[6]

Study appraisal

Risk of bias per trial: Each trial was assessed against seven pre-defined judgmental criteria[2]: *domain I*, the method used to generate the random sequence; *domain II*, the method of allocation concealment used to implement the random sequence; *domain IIIA*, the blinding of trial personnel, including animal owner as appropriate; *domain IIIB*, the blinding of outcome assessors; *domain IV*, whether all the randomised patients are accounted for in the analysis; *domain V*, whether there is evidence of selective outcome reporting[a]; *domain VI*, whether there is evidence of other bias, such as extreme data imbalance at baseline.[7]

An overall classification of 'low risk of bias', 'uncertain risk of bias' or 'high risk of bias' was then applied to each trial. A trial with overall low risk of bias comprised 'reliable evidence'. For a trial that did not display high risk of bias, we regarded its evidence as *reliable* if the study was assessed as free of bias for each of domains I, IIIA, IIIB and IV. Finally, importance was placed on trials with reliable evidence and were not explicitly funded, directly or indirectly, by a homeopathic pharmacy (there was no overt vested interest in the trial's findings).[2]

Outcome assessment and reporting

As previously described,[2] for each trial we identified the 'main outcome measure' using a refinement of approaches adopted by others.[8,9]

Meta-analysis

Summary measures for 'main outcome': For each eligible trial, the 'effect size' was taken as the difference between the homeopathy and the placebo groups at our pre-determined end-point of the trial, as follows[10]:

- For **dichotomous measures**: odds ratio (OR), with 95% confidence interval (CI);
- For **continuous measures**: standardised mean difference (SMD), with 95% CI.

If the original paper did not provide adequate information on our designated main outcome measure to enable data extraction for meta-analysis, we described that trial's outcome as 'not estimable': a further, estimable, outcome was not sought.

All calculations and analyses were performed using Review Manager 5.2 (Cochrane Collaboration). Given our anticipation of heterogeneous data for intervention effects, the random-effects (rather than fixed-effects) model was used for all meta-analyses.[5] For meta-analyses requiring the merging of dichotomous and continuous data, we re-expressed SMD of relevant RCT data as OR.[5,11]

Hypothesis-driven analysis: For all species per category we aimed to determine summary statistics for:

[a] No study protocol existed for any of the studies: domain V was assessed as described in Reference 2. For the purposes of the current paper, we would have been entitled to reassess a trial as high risk of bias in domain V if the main outcome data were not extractable for meta-analysis; however, to ensure a unified approach with that of Reference 2, we opted not to carry out such reassessment.