Meta-Analysis of Longitudinal Data: Effect of Oral Selenium Supplementation on Milk Selenium Concentration in Cattle

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ABSTRACT

Soils in several regions of the world have low selenium (Se) content; consequently, pastures and crops grown on these soils often provide inadequate dietary Se for pasture-based animals. Milk Se concentration is an indicator of Se status, and reflects the responsiveness to supplementation; however, the results of Se supplementation trials are still controversial. Meta-analysis of longitudinal studies reports the treatment effects as a single summary; however, meta-analytic models can be extended to account for correlated data. The objective was to conduct a systematic review and a meta-analysis to summarize all available scientific evidence of the effect of oral Se supplementation on milk Se concentration in cattle, presenting an approach to handling correlations inherent to longitudinal data. Analyses were carried out using mixed models where observations were clustered within studies and repeated over time. Different correlation structures were compared by likelihood-ratio tests. A literature search based on electronic and non-electronic databases delivered 90 studies that provided useful data to perform the meta-analysis. The follow-up period ranged between 12 and 270 days, and the number of sampling periods ranged from 1 to 4. The independence model produced and average effect for oral Se supplementation on milk Se concentration of 0.21 (95% CI: -0.41, 0.83) µmol/L, while accounting for correlations between and within-study produced an average effect of 0.32 (95% CI: 0.27, 0.38) µmol/L. Se-yeast had a larger effect compared to sodium selenite/selenate. There is still a significant amount of unexplained between study heterogeneity, which might indicate that other study-level factors are influencing the milk Se concentration. The meta-analytic model is now being extended to account for dependence between correlated data, which might provide a better fit of the model, and provide more precise estimates.

INTRODUCTION

Soils in several regions of the world have low selenium (Se) content; consequently, pastures and crops grown on these soils often provide inadequate dietary Se for pasture-based animals. Recent surveys in various countries have indicated a significant proportion of cattle receive inadequate dietary Se, with low Se intake being associated with several economically important diseases, such as mastitis and retained placenta (Wichtel, 1998). Milk Se concentration is a useful indicator of animal or herd Se status, and can help to predict responsiveness to supplementation; however, the results of Se supplementation response trials to improve Se status and milk Se concentration are conflicting.

Narrative reviews have been widely used in veterinary literature to collate existing evidence on a particular intervention. The majority of them do not use either a systematic or statistical method to identify, assess, and synthesize the information, and are based on preconceived opinions of the reviewer (Sargeant et al., 2006). A systematic process appraises critically, summarizes and attempts to reconcile all published evidence concerning to a particular intervention, minimizing errors. It may or may not include a quantitative analysis (meta-analysis) of the results to produce an average estimate of the treatment effect (Jadad et al., 1998).

Longitudinal studies are used to assess the effect of an exposure or intervention over time, typically involving measurements of the outcome at pre-determined intervals (Ishak et al., 2007). Meta-analysis of longitudinal studies usually reports the treatment effects as a single summary by averaging all time points into a single effect estimate for each study (DerSimonian and Laird, 1986). However, special consideration is required since the effect estimates at different time points are inherently correlated. Another challenge to meta-analyze longitudinal data is that the timing of repeated measures and the number of missing data vary across trials, both at the study level. A few examples of longitudinal meta-analysis have been recently published (Maas et al., 2004; Ishak et al., 2007; Jones et al., 2009), but in veterinary medicine there are no methodological references published to date. Because no references on longitudinal meta-analysis have been published in veterinary medicine, the objective of this study was to conduct a systematic review and a meta-analysis to summarize all available scientific evidence of the effect of oral Se supplementation on milk Se concentration in cattle, at the same time presenting an approach to handling correlations inherent to longitudinal data.

MATERIAL AND METHODS

All details related to the literature search to identify primary studies, keyword combinations, covered databases, selection and exclusion criteria, and data extraction were described previously (Ceballos et al., 2009). The mean difference in milk Se concentration (µmol/L) between Se-supplemented and unsupplemented cows was the outcome of interest.

A multivariate model was developed where observations were clustered within studies and repeated over time (Maas et al., 2004; Ishak et al., 2007). The model had the following specifications: random study-effects, correlations within and between studies were allowed, and complete independence between random-effects and residuals was assumed. The following model gives the observed difference in milk Se concentration of i^{th} study at time j, accounting for the correlations between the observations:

$$y_{ij}=ß_{0i}+ß_1 time_i+ ß_2 source_i+ß_3 time_* source_i+\upsilon_{0i}+ \upsilon_1 time_i+\varepsilon_{ij},$$

where y_{ij} corresponds to the observed value from the i^{th} study at time j, $ß_0$ corresponds to the intercept of the study; $ß_1$ and $ß_2$ correspond to the effect of time and source of Se on the observed value, respectively; υ_0 is the random effect of the study; υ_1 is the random study effect of time on the observed value; and ε_{ij} is the error term at the within-study level.

The meta-analysis of longitudinal data requires some assumptions in order to limit the number of parameters added to the model (Ishak et al., 2007). Thus it was assumed a constant within-study correlation across studies, which means that the correlation for two time points was the same in two different studies; however, the between-study variances were allowed to differ. The between-study variances were calculated from univariate analysis. Further a single-parameter correlation structure was adopted (i.e. heterogeneous autoregressive). Both models, complete independence and multivariate, were compared by likelihood-ratio tests and Akaike's information criteria (AIC). The models also included categorical effects of source of Se and the interaction with time. Estimations were performed using the procedure PROC MIXED of SAS version 9.1.3 (SAS Institute Inc, Cary, NC, USA).

RESULTS AND DISCUSSION

The literature search was based on electronic and non-electronic databases, 64 studies, grouping 93 observations, provided data that fulfilled all criteria, and were used to perform the meta-analysis. The follow-up period in these studies ranged between 12 and 270 days. Samples were collected, on average, in 1.5 time points ranging between 1 and 4. Several studies reported the effects at some but not all time points, therefore the unreported effects were treated as missing values (Ishak et al., 2007). The estimations in this meta-analysis were restricted to two different models, one assuming complete independence and the other one accounting for the correlation between observations.

The interaction between time, which is the number of days from the beginning of treatment to sample collection, and the source of Se was highly significant in the multivariate model (Figure 1; P<0.01).

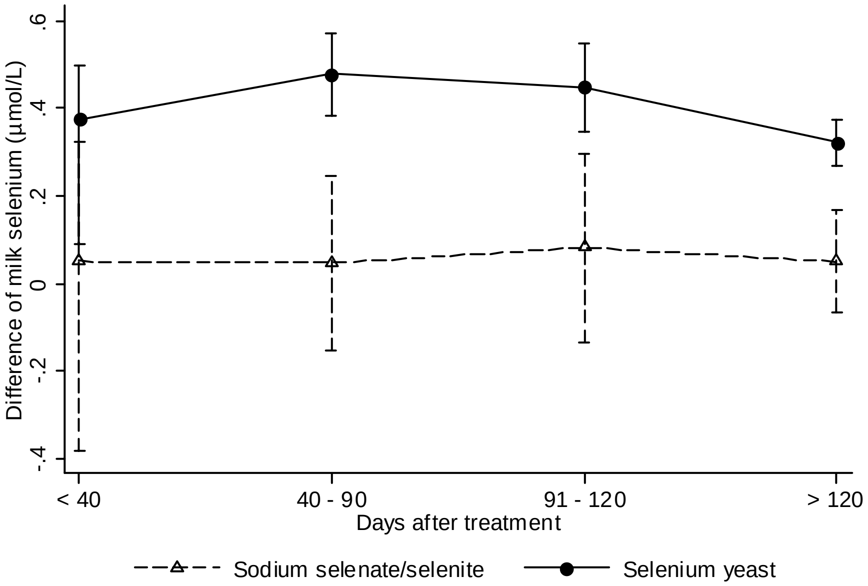

Figure 1. Effect of the source of selenium on the difference of milk selenium concentration (µmol/L) plotted against the time intervals from the beginning of supplementation to sample collecting.

Meta-analytic models that account for the correlation between observations appear to have a better fit than the independence model, producing an average effect with narrower confidence intervals, which agrees with Ishak et al. (2007), who also suggested that the use of a linear mixed model for meta-analyze longitudinal data will produce a more precise estimate for those time-points where data are limited. The estimates for the between-study variance, correlations and model fit are presented in Table 1.

Table 1. Between-study variance estimates, within- and between-study correlation estimates, and model comparison in two models for meta-analysis of longitudinal data.

Factor	Complete independence	Multivariate model
Time intervals (days)[1]:		
<42	-0.1023 [-0.7114, 0.5069]	0.0520 [-0.0183, 0.1224]
42-90	-0.0996 [-0.7310, 0.5319]	0.1544 [0.1154, 0.1933]
91-120	0.2470 [-0.5961, 1.0902]	0.1246 [0.0780, 0.1712]
> 120	Baseline	Baseline
Source of selenium:		
Sodium selenate/selenite	0.0390 [-0.0276, 0.1055]	0.0506 [0.0167, 0.0845]
Selenium yeast	0.2139 [-0.3943, 0.8222]	0.3230 [0.2701, 0.3759]
Estimates of correlations:		
Within-study	NA[2]	0.99
Between-study	NA[2]	0.96
Model fit:		
Log likelihood	54.4	-67.7
AIC	56.4	-55.7

[1]Days from the beginning of treatment.
[2]Model does not include correlation parameters.

Both models indicated that the difference in milk Se concentration increased over time, and cows supplemented with Se yeast had a higher milk Se concentration compared to those cows supplemented with an inorganic source of Se (sodium selenate/selenite). The results of this approach to meta-analyze longitudinal data are similar to another meta-analytic approach to evaluate the evidence of the effect of oral Se supplementation on milk Se concentration in cattle (Ceballos et al., 2009).

CONCLUSION

The meta-analytic model may be extended now to account for dependence between correlated data, which might provide a better fit of the model, and a more precise estimation of the average effect. This model may produce different results from traditional approaches used to meta-analyze longitudinal data (i.e. grouping or aggregating data), which is indicating that more simulation studies are required. A multivariate model approach to meta-analyze the collected evidence indicated that oral Se supplementation significantly increased milk Se content. There is still a significant amount of unexplained between study heterogeneity, which might indicate that other study-level factors are influencing the milk Se concentration.

REFERENCES

Ceballos, A., Sanchez, J., Stryhn, H., Montgomery, J.B., Barkema, H.W., Wichtel, J.J. (2009) Meta-analysis of the effect of oral selenium supplementation on milk selenium concentration in cattle. *Journal of Dairy Science*, 92, 324-342.

DerSimonian, R., Laird, N. (1986) Meta-analysis in clinical trials. *Controlled Clinical Trials*, 7, 177-188.

Ishak, K.J., Platt, R.W., Joseph, L., Hanley, J.A., Caro, J.J. (2007) Meta-analysis of longitudinal studies. *Clinical Trials*, 4, 525-539.

Jadad, A.R., Cook, D.J., Jones, A., Klassen, T.P., Tugwell, P., Moher, M., Moher, D. (1998) Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals. *Journal of the American Medical Association*, 280, 278-280.

Jones, A.P., Riley, R.D., Williamson, P.R., Whitehead, A. (2009) Meta-analysis of individual patient data versus aggregate data from longitudinal clinical trials. *Clinical Trials*, 6, 16-27.

Maas, C.J.M., Hox, J.J., Lensvelt-Mulders, G.J.L.M. (2004) Longitudinal meta-analysis. *Quality & Quantity*, 38, 381-389.

Sargeant, J.M., Rajic, A., Read, S., Ohlsson, A. (2006) The process of systematic review and its application in agri-food public-health. *Preventive Veterinary Medicine*, 75, 141-151.

Wichtel, J.J., (1998) A review of selenium deficiency in grazing ruminants. Part 1: New roles for selenium in ruminant metabolism. *New Zealand Veterinary Journal*, 46, 47-52.