Ascorbic acid for anemia management in hemodialysis patients: a systematic review and meta-analysis


CRD summary
The authors concluded that despite limitations with the trials, ascorbic acid may provide short-term improvements in haemoglobin concentrations and transferrin saturations and decrease recombinant human erythropoietin doses in haemodialysis patients compared to standard care alone. Given the small number of poor quality and variable trials, the findings should be interpreted with caution; the recommendation for further research seemed appropriate.

Authors' objectives
To assess the efficacy and safety of adding ascorbic acid to standard anaemia management in patients receiving haemodialysis.

Searching
PubMed (from 1966) and EMBASE (from 1980) were searched to October 2008 and Cochrane Central register of Controlled Trials (CENTRAL) was searched in 2008 without language restrictions. Search terms were reported. Reference lists of identified citations and conference proceedings of American Society of Nephrology (to 2007) were searched.

Study selection
Randomised controlled trials (RCTs) that assessed the effects of ascorbic acid in addition to standard anaemia management in patients who received haemodialysis were eligible for inclusion. Cross-over designs were eligible if initial treatment allocation was randomised. The primary outcome of interest was change in mean haemoglobin concentration (g/dL). Secondary outcomes included change in mean recombinant human erythropoietin (rHuEPO) dose (units/kg/week), change in mean ferritin concentration (μg/L), change in transferrin saturation (%) and adverse events. Trials that used a fixed dose of rHuEPO throughout the trial were excluded.

Where reported, included trials were of patients with a mean age range from 41.1 to 60.0 years. Most trials administered 500mg ascorbic acid intravenously; one trial administered this orally and single trials each administered 200mg or 300mg intravenously. Most trials administered ascorbic acid three times per week; one trial administered once a week. Iron and recombinant human erythropoietin (rHuEPO) protocols differed between trials. Controls received standard care. Study duration ranged from two to six months. All patients received concomitant erythropoietin therapy. The main aim of all trials was the effect of ascorbic acid on erythropoiesis.

Two reviewers independently assessed studies for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed study quality based on criteria of randomisation, allocation concealment, blinding, intention-to-treat (ITT) analysis and loss to follow-up.

Data extraction
It seemed that two reviewers independently extracted change in outcome data from baseline to end of follow-up and extracted or calculated standard deviations (SDs). Where haemocrit values were reported, these were converted to haemoglobin concentration. Where rHuEPO doses were reported in units per week, these were standardised to units per kilogram per week. Primary authors were contacted for additional information, where necessary.

Methods of synthesis
For each outcome, random-effects models were used to pool mean differences in order to calculate weighted mean differences (WMDs) and 95% confidence intervals (CIs). Only studies with mean baseline haemoglobin levels of less than 11 g/dL were included in the analysis. Only the initial treatment period from crossover trials was used.
Statistical heterogeneity was assessed using the $I^2$ statistic. Sensitivity analysis was conducted by removal of trials that administered ascorbic acid orally.

Publication bias was assessed using Begg’s and Egger’s tests.

**Results of the review**

Six RCTs (n=326, range 18 to 153) were included in the review: four parallel and two cross-over designs. The quality of the RCTs was generally poor; two reported the randomisation process and only one of these reported allocation concealment. Only one RCT reported blinding. All trials used intention-to-treat analysis. Loss to follow-up ranged between 0% and 28%.

There were statistically significant improvements in patients who received ascorbic acid compared to controls for haemoglobin concentration (WMD 0.9g/dL, 95% CI 0.5 to 1.2; three RCTs, n=125) and transferrin saturation (WMD 7.9%, 95% CI 5.2 to 10.5; five RCTs, n=173). rHuEPO dose was statistically significantly reduced in patients who received ascorbic compared with controls (WMD -17.1 U/kg/wk, 95% CI -26.0 to -8.2; five RCTs, n=303). There was no statistically significant difference in ferritin concentration between patients who received ascorbic acid or control (five RCTs, n=266). There was no evidence of significant statistical heterogeneity for any comparisons. Sensitivity analysis did not alter the results significantly.

Adverse events were poorly reported in the included trials and had questionable relevance to the use of ascorbic acid. Details were reported in the review.

There was no evidence of publication bias using Begg’s and Egger’s tests.

**Authors’ conclusions**

Ascorbic acid provided short-term improvements in haemoglobin concentrations and transferrin saturations and a decrease in rHuEPO doses compared to standard care in haemodialysis patients. There were limitations with the included trials and further research was required.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The literature search was adequate and was not restricted by language, which minimised potential for language bias. Formal assessment of publication bias showed no evidence of bias. Each stage of the review process was undertaken in duplicate, which reduced potential for reviewer error and bias. Trial quality was assessed using appropriate criteria. The included trials were of poor quality. The authors acknowledged the small number of included trials, heterogeneity among trial populations, short study durations and limitations with some of the individual trials. There also appeared to be some methodological heterogeneity, which suggested that pooling of the results may not have been appropriate. There was no evidence of statistical heterogeneity.

This was a generally well-conducted review, but limitations with the included studies mean that the findings should be interpreted with caution. The authors’ suggestion for further research seemed appropriate.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** the authors stated that large good-quality long-term trials that included clinical endpoints were needed to corroborate the short-term results and provide better information on adverse events.

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