Comparison of intermittent intravenous and oral calcitriol in the treatment of secondary hyperparathyroidism in chronic hemodialysis patients: a meta-analysis of randomized controlled trials

Zhou H, Xu C

CRD summary
This review found that there were no significant differences between intermittent intravenous and oral calcitriol in the treatment of secondary hyperparathyroidism for efficacy or adverse reactions. These conclusions should be interpreted with some caution given the possibility of publication bias and the poor quality and small size of the included trials.

Authors' objectives
To compare intravenous and oral administration of intermittent calcitriol in the treatment of secondary hyperparathyroidism in chronic haemodialysis patients.

Searching
MEDLINE, EMBASE, Chinese Biological Medicine Disk and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to February 2008. Search terms were reported. References of primary studies and reviews were screened. No language restrictions were applied. Studies available only as abstracts were excluded.

Study selection
Randomised controlled trials that compared oral with intravenous administration of intermittent calcitriol in patients with secondary hyperparathyroidism (according to established diagnostic criteria), were eligible for inclusion. Secondary hyperparathyroidism diagnosis was defined as patients in which baseline parathyroid hormone was at least three times above the normal range. Eligible trials also had to report data on parathyroid hormone before and after the intervention. Trials in which patients were receiving peritoneal dialysis were excluded, as were those in which patients received other vitamin D drugs or medications which may interfere with vitamin D and/or bone homeostasis.

Outcomes of interest were intact parathyroid hormone, serum alkaline phosphatase, serum total calcium, serum phosphorus, incidence of hypercalcaemia, incidence of hyperphosphatemia, calcitriol-related death, and other adverse events.

In included trials, the mean age of participants ranged from 40 to 58 years and their baseline parathyroid hormone values ranged from 310 to 1979 pg/mL. Calcitriol dose ranged from 2.0 to 6.1 μg/week; doses were similar for intravenous and oral modes of administration. Trial duration ranged from 10 to 24 weeks.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed trial quality using the Jadad scale, which assessed randomisation, blinding and description of withdrawals and drop-outs. Trials were assigned a score up to a maximum of 5 points. Disagreements were resolved through discussion.

Data extraction
Two reviewers independently extracted data as the mean and standard deviation for baseline and final values for continuous outcomes. Data were extracted as the number of events and number of participants for dichotomous outcomes and used to calculated odds ratios. Disagreements were resolved through discussion. Where necessary, authors were contacted for additional information.

Methods of synthesis
Weighted mean differences, together with 95% confidence intervals, were pooled. If baseline values were homogenous, the mean difference comparing the final values between groups was calculated, otherwise mean differences in changes between baseline and final values comparing treatment and control groups were calculated. Pooled odds ratios, together
with 95% confidence intervals, were estimated using the Peto method. If significant heterogeneity was present, random-effects models were used. Heterogeneity was assessed using the Q and $I^2$ statistics. Sensitivity analysis was conducted to determine the effects of secondary hyperparathyroidism severity.

**Results of the review**
Six parallel group RCTs (n=174) were included in the review. Trials were of low quality with Jadad scores ranging from 1 to 2. None of the trials reported double blinding, all scored 1 point for randomisation and two RCTs scored zero for withdrawals.

There were no statistically significant differences between intravenous and oral calcitriol for any of the continuous outcomes assessed for efficacy (suppressing intact parathyroid hormone and serum alkaline phosphatase) or for adverse effects (rising serum calcium and phosphorus).

Dichotomous data were not pooled due to insufficient and heterogeneous data. Three RCTs reported no hypercalcaemia during the trial, two RCTs reported no difference in hypercalcaemia between the treatment groups, and one RCT reported significantly greater hypercalcaemia in the oral group (eight of 12 patients) compared with the intravenous group (none of 13 patients). Only two RCTs assessed hyperphosphataemia; one reported no cases during the trial, the other reported no significant difference in incidence across treatment groups. There were no calcitriol related deaths in any trial. Stratifying the analysis based on secondary hyperparathyroidism severity did not alter the results.

**Cost information**
One trial reported data on cost and found that intravenous administration was much more expensive than oral administration.

**Authors’ conclusions**
There were no significant differences between intermittent intravenous and oral calcitriol in the treatment of secondary hyperparathyroidism for efficacy or adverse reactions.

**CRD commentary**
The review addressed a focused question supported by clearly defined inclusion criteria. The literature search was adequate for published studies, but specific attempts were not made to identify unpublished studies, so publication bias was a possibility. Appropriate steps were taken to minimise bias and errors in data extraction and quality assessment, but it was unclear whether such steps were also taken in the selection of studies.

Trial quality was assessed using appropriate criteria and the results were clearly presented. The methods of analysis were appropriate and results were clearly presented using forest plots.

The authors conclusions' are supported by the data presented, but should be interpreted with some caution given the possibility of publication bias and poor quality and small size of the included trials.

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

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

**Research**: The authors stated that there is a need for large-scale, long-term, double blind, randomised placebo-controlled trials to compare intermittent intravenous and oral calcitriol treatment.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.