Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death

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CRD summary
This review evaluated low-dose dopamine, compared with placebo or no treatment, in patients with or at risk of kidney failure. Dopamine was associated with transient improvements in kidney function but no benefit in clinical outcomes. The authors’ conclusions appear generally reliable. Most of the participants received dopamine for the prevention of kidney failure, and the findings may not be applicable beyond this group.

Authors' objectives
To evaluate treatment with low-dose dopamine, compared with placebo or no treatment, in patients with or at risk of acute renal failure.

Searching
The authors searched MEDLINE, EMBASE and CINAHL (from inception to early 2005), the Cochrane CENTRAL Register (Issue 4, 2004), the Renal Health Library (February 2005) and Cancerlit (from 1975 to October 2002). Two independent search strategies were used and the search terms used were reported. There were no language restrictions. The reference lists of retrieved articles and of recent review articles were screened to identify additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-randomised trials were eligible for inclusion. Studies with pharmacological cointerventions that were applied to both groups were eligible.

Specific interventions included in the review
Studies of low-dose dopamine (5 microg/kg body weight per minute or less) compared with placebo or no therapy were eligible for inclusion. The doses in the included studies ranged from 1 to 5 (median 2.5) microg/kg body weight per minute, and the duration of administration ranged from less than 1 hour to 8 days (median 31 hours).

Participants included in the review
Patients with or at risk of acute renal failure were eligible for inclusion. The participants in included studies were patients undergoing cardiac, vascular or other surgery, patients receiving intravenous contrast dye, patients receiving other nephrotoxic medications, neonates and patients with other miscellaneous indications. Most of the participants were at risk of renal failure from a surgical or pharmacological intervention and were given dopamine for prevention; only 6 trials had participants who were treated therapeutically for acute renal failure.

Outcomes assessed in the review
Studies were eligible for inclusion if they recorded all-cause mortality, requirement for renal replacement therapy, renal physiological variables (urine output, serum creatinine or measured creatinine clearance) or adverse events (AEs). Arrhythmias, myocardial ischaemia, and limb or cutaneous ischaemia were defined a priori as AEs of interest likely to be detected by routine patient monitoring.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for relevance. Any disagreements were resolved by consensus.

Assessment of study quality
Validity was assessed on the basis of the method of treatment allocation and whether allocation was concealed, blinding...
of the caregivers and outcome assessors, and the number of and reasons for withdrawal after randomisation. Two reviewers independently assessed the studies for validity. Any disagreements were resolved by consensus. The reviewers attempted to contact all study authors, either to clarify methodological information or for additional outcome data.

Data extraction
Two reviewers independently extracted the data from the included studies. Any disagreements were resolved by consensus. The reviewers attempted to contact all study authors, either to clarify methodological information or for additional outcome data. For binary outcomes, the number of events in each group was used to calculate a relative risk (RR) and associated 95% confidence interval (CI). For continuous outcomes, the treatment effect was expressed as the ratio of the mean value in the dopamine group to the mean value in the control group. A standard error was calculated for the natural logarithm-transformed ratio.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis using a random-effects model. For binary outcomes, a summary RR was calculated on a natural logarithm scale. The studies were weighted according to the inverse of the variance of the natural logarithm of the RR. For studies with no events in one arm, 0.5 was added to all cells. For continuous outcomes, the ratio of the mean value in the dopamine group to the mean value in the control group was transformed to a natural logarithm and aggregated across studies using the generalised inverse variance method. Funnel plots of standard error against treatment effect were used to investigate publication bias.

How were differences between studies investigated?
Heterogeneity was assessed using the Cochran Q-test, with a P-value of 0.1 or less indicating significant heterogeneity, and the I-squared statistic; heterogeneity was considered substantial if I-squared exceeded 50%. Several potential sources of statistically significant heterogeneity (patient population, baseline risk, dose, duration of therapy, adequacy of allocation concealment and blinding of caregivers) were identified a priori. Differences in estimates of treatment effects between subgroups differing for these factors were tested using a Z-test, with a P-value of 0.05 or less being considered statistically significant.

Results of the review
Sixty-one studies with 3,359 participants were included in the review: 52 RCTs (2,993 participants) and 9 quasi-randomised trials (366 participants).

There were no significant differences between the dopamine and control groups for mortality (pooled RR from 15 trials, 0.96, 95% CI: 0.78, 1.19), need for renal replacement therapy (pooled RR from 12 trials, 0.93, 95% CI: 0.76, 1.15), or pre-specified AEs (pooled RR from 50 trials, 1.13, 95% CI: 0.90, 1.41). There was no evidence of heterogeneity for these outcomes. The pooled analysis showed an increase in urine output on the first day after starting low-dose dopamine (ratio of means 1.24, 95% CI: 1.14, 1.35, P<0.001), but the difference between groups was no longer significant on days 2 or 3. Serum creatinine level decreased significantly (ratio of means 0.96, 95% CI: 0.93, 0.99, P=0.01) and creatinine clearance increased significantly (ratio of means 1.06, 95% CI: 1.01, 1.11, P=0.02) on day 1 in the dopamine group relative to the control group. Neither difference was significant after day 1. With the exception of day 1 creatinine clearance, significant between-study heterogeneity was present for all renal physiological outcomes. In most cases the heterogeneity was not explained by the pre-specified factors. Statistically significant results of the Z-test for sources of heterogeneity were related to study methods (blinding for three outcomes and allocation concealment for one), with the blinded and concealed trials giving more conservative estimates of treatment effect.

Funnel plots did not suggest the presence of publication bias. Inter-rater agreement for selecting studies for inclusion was high (K=0.98, 95% CI: 0.96, 1.00).

Authors' conclusions
Therapy with low-dose dopamine was associated with transient improvements in renal physiology, but there was no
evidence of a benefit in clinical outcomes.

**CRD commentary**
The research question and the inclusion criteria were clearly stated, although the criteria for participants were very broad. The authors searched a range of databases without language restrictions and contacted study authors for further details as necessary. A possible limitation of the search was that the authors made no attempt to identify unpublished studies, but funnel plots were used to assess the risk of publication bias. Validity was assessed and taken into account as a possible source of heterogeneity in the review. The study selection, validity assessment and data extraction were performed by two independent reviewers, thus reducing the risk of bias or errors during the review process.

Details of the included studies were provided in tabular format and on the journal's website. The authors used standard methods for the meta-analysis and justified their choice of outcome measures. Heterogeneity was assessed and the reasons for it investigated using analyses specified in advance. This was a well-conducted review and the authors’ conclusions appear generally reliable. Most of the participants received dopamine for the prevention of renal failure; the findings may be more robust for this group than for those who received dopamine therapeutically.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that an extremely large RCT would be required to demonstrate the benefits, if any, in clinical outcomes from low-dose dopamine therapy.

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**Other publications of related interest**
This additional published commentary may also be of interest. Qushmag I. Review: low-dose dopamine does not reduce mortality or need for renal replacement therapy. ACP J Club 2005;143:42.

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Subject indexing assigned by NLM

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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.