Urokinase lock or flush solution for prevention of bloodstream infections associated with central venous catheters for chemotherapy: a meta-analysis of prospective randomized trials

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CRD summary
This review concluded that use of urokinase lock solution in high-risk patients being treated with long-term central intravascular devices may reduce the risk of bloodstream infections. Clinical heterogeneity coupled with the probability of publication and the general low quality of the included studies means that the reliability of the authors' cautious conclusions is open to some doubt.

Authors' objectives
To assess the use of urokinase compared to heparin for the prevention of blood stream infections in patients with long-term intravascular devices.

Searching
PubMed, Current Contents, CINAHL, DARE, The Cochrane Library, Conference Papers Index and BIOSIS RRM were searched from inception to January 2007. Search terms were reported. Abstracts of four relevant scientific meetings were searched from 1998 to 2005. An internet search was undertaken and clinicaltrials.gov was checked for ongoing trials. References of identified studies were checked. It appeared that no language restrictions were applied (although conflicting statements on this issue appeared in the publication).

Study selection
Randomised controlled trials (RCTs) that compared catheter installation of urokinase with placebo or standard care and reported bloodstream infections were eligible for inclusion in the review.

All included studies enrolled patients with haematological malignancies; two studies enrolled only children. Two studies used only subcutaneous ports, two used only tunneled intravascular devices and one study used both. Either flush solutions or lock solutions were used. Incidence of thrombosis or catheter occlusion and adverse effects were reported in some of the included studies. Criteria for diagnosis of bloodstream infections varied between studies. Duration of treatment and doses and regimens involved varied widely.

Two authors independently assessed the studies for inclusion; disagreements were resolved through discussion.

Assessment of study quality
The authors did not state that they assessed validity, but details of the randomisation scheme, blinding and whether intention-to-treat analysis was employed were extracted for each study.

Data extraction
Data to permit the calculation of relative risks (RR) with 95% confidence intervals (CI) were extracted using a standardised form.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled relative risks with 95% CI were calculated using both the DerSimonian and Laird random-effects model and the Mantel-Haenszel fixed-effect model. Heterogeneity was assessed using Cochran's Q and the $I^2$ statistic. Subgroup analyses were used to explore heterogeneity. Publication bias was assessed using funnel plot analysis and Egger's test.

Results of the review
Five RCTs (n=991) were included in the review. Two trials reported appropriate randomisation; only one was double-
blinded and only one used an intention-to-treat analysis

Incidence of bloodstream infections was lower in groups treated with urokinase compared to the comparator groups (fixed effect RR 0.74, 95% CI 0.58 to 0.94). This did not change significantly with a random-effects model analysis. Statistical heterogeneity was not statistically significant ($I^2=0\%$, Q statistic $p=0.53$). Three trials reported venous thrombosis or catheter occlusion and one found a statistically significant reduction in catheter occlusion in the urokinase group. Four of the five studies reported on adverse effects; three reported no adverse consequences of urokinase and one reported adverse effects that were mainly related to underlying disease or concomitant chemotherapy. There was evidence that publication bias was present.

Cost information
One study found that the addition of daily prophylactic urokinase added $3,398 per patient.

Authors' conclusions
Use of urokinase lock solution in high-risk patients being treated with long-term central intravascular devices may reduce the risk of bloodstream infections.

CRD commentary
The review question and inclusion criteria were clear. The authors searched a number of relevant databases and other sources and it appeared that no language restrictions were employed. This reduced the chances that relevant studies were omitted and that language and publication biases were introduced into the review. Assessment revealed that publication bias was present. The authors reported that they used methods designed to reduce reviewer bias and error in study selection, but not in the extraction of data, which included some limited appraisal of characteristics associated with study validity. There was considerable clinical heterogeneity between studies, although this was not accompanied by significant statistical heterogeneity.

Clinical heterogeneity, coupled with the probability of publication bias and the general low quality of the included studies means that the reliability of the authors' cautious conclusions is open to some doubt (which they acknowledged).

Implications of the review for practice and research
Practice: The authors stated that consideration should be given to use of a urokinase lock for prevention of bacteraemia in high-risk vulnerable patients.

Research: The authors stated that a large RCT was required to determine the role of urokinase for prevention of bloodstream infections associated with intravascular devices. There was a need for future studies to identify optimum doses and regimens of urokinase in order to reduce costs and limit adverse effects.

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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.