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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Abstract: Background: Intravascular devices (IVDs) carry significant risk of device-associated bloodstream infection (BSI). Catheter thrombosis increases the likelihood of microbial colonization of the catheter and BSI. Urokinase has been studied for the prevention of BSI associated with IVDs. We undertook a systematic review to determine the efficacy of urokinase-heparin lock or flush solution compared with heparin alone in preventing IVD-associated BSI.

Methods: Computerized databases were searched for relevant publications in English from January 1966 to 1 January 2007. We identified randomized controlled trials comparing a urokinase-heparin lock or flush solution with heparin alone for prevention of BSI associated with long-term IVDs. Summary effect sizes were calculated with assessment of heterogeneity.

Results: Five randomized, controlled trials involving a total of 991 patients being treated with IVDs met the inclusion criteria; all five studies were conducted among patients with cancer; three of these studies were undertaken in children and two in adults. The summary risk ratio with a urokinase-heparin lock solution for IVD-associated BSI was 0.77 (95% confidence interval [CI], 0.60–0.98; p=0.01). Results of the test for heterogeneity were not statistically significant (p=0.53).

Conclusions: Use of a urokinase lock solution in high-risk patient populations being treated with long-term central IVDs may reduce the risk of BSI. However, there are few randomized trials and methodologic limitations of these preclude more robust recommendations regarding the use of urokinase to prevent BSI. Further adequately powered studies should seek to evaluate the efficacy of urokinase and optimize dosage and instillation regimen.

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Key words: Urokinase, Catheter infection, Cancer and bloodstream infection

INTRODUCTION

Prolonged central venous access is essential in critically ill neonates requiring parenteral alimentation and children and adults requiring intensive cancer chemotherapy, bone marrow or solid organ transplants, home antibiotic therapy, or lifelong hemodialysis or total parenteral nutrition (1-3). Upwards of 5 million US patients require prolonged central venous access each year (4, 5). The intravascular devices (IVDs) available for long-term central access include cuffed and tunneled central venous catheters, subcutaneous ports and peripherally-inserted central venous catheters (PICCs) (4). Although reliable, these devices are, nonetheless, associated with a considerable risk of IVD-associated thrombosis and bloodstream infection (BSI) (4, 5). Device-associated BSIs increase antibiotic exposure, length of stay (6-9), healthcare costs (6, 8, 9), and mortality (6, 7, 9, 10). Thirty to forty percent of patients with long-term central venous catheters used for parenteral alimentation or chemotherapy develop device-associated thrombosis of the deep veins (11, 12). Several studies have found device-associated thrombosis and occlusion to increase the risk of device-associated BSI (13-16).
Urokinase, a thrombolytic agent derived from human kidney cells, has been investigated as a measure to prevent central venous catheter (CVC) thrombosis and bloodstream infection (17-20). Some but not all studies have found benefit to using urokinase for prevention of IVD-related BSI. We report a meta-analysis of prospective randomized trials evaluating the use of urokinase when compared to heparin for the prevention of BSI in patients with long-term IVDs.

METHODS

We performed a computerized search of PUBMED (including MEDLINE), CURRENT CONTENTS, CINAHL, DARE and the COCHRANE NETWORK from inception until January 2007. We used the following key words alone and in combinations: urokinase, thrombolytics, catheter related bacteremia, prophylaxis, prevention, intravascular device related infections, central venous catheters, bacteremia and bloodstream infections. In addition, we searched the following conference abstract databases: Conference Papers Index and BIOSIS RRM. Abstracts of meetings of the American Society of Clinical Oncology (ASCO), InterScience Conference on Antimicrobial Agents and Chemotherapy, the Infectious Diseases Society of America, and European Society of Intensive Care Medicine (1998-2005) were also reviewed. We repeated the search with the same keywords using Google search engine (http://www.google.com). We reviewed National Institutes of Health Website listings of ongoing trials (http://www.clinicaltrials.gov), and contacted authorities in the field for identification of additional unpublished studies. Reference lists of articles were searched to identify additional articles. No language restrictions were placed on the search. Articles were included in our review if they met the following criteria: randomized controlled trials that compared catheter instillation of urokinase with placebo or standard care and reported BSI as an outcome. We excluded non-randomized trials, case reports, review articles, letters and editorials. Both authors independently reviewed each report identified by the above mentioned search strategy. Disagreements among abstracters regarding values or assignment of studies were resolved by discussion. The QUORUM checklist was followed for study selection, data abstraction, data synthesis and reporting of results (21).

Data abstraction and statistical analysis

Data were extracted using a standard form for each relevant study and included the total number of patients in the study, those randomized to urokinase and the comparator, details regarding the randomization scheme, concentration and method of instillation of urokinase, patient population, duration of catheter implantation, adverse effects of urokinase, method of diagnosis and incidence of BSI. Data on incidence of BSI were abstracted as dichotomous variables. We used the patient as the unit of analysis for the incidence of IVD-related BSI and mortality. Whenever necessary, authors of included articles were contacted to obtain additional information required for the statistical analysis. Studies were classified based on whether or not intention-to-treat analysis was used. Pooled estimates of the RR and 95% confidence interval (95% CI) were obtained using the DerSimonian and Laird random effects model (22) and the Mantel-Haenszel fixed effects model (23). Heterogeneity was assessed using the Cochran Q statistic and I², \([100\% \times (Q-df)/Q]\), where Q is Cochran’s Q statistic and df is degrees of freedom (24). Degrees of freedom are equal to k-1 where k is the number of studies. Negative values of I² are put equal to 0%, so I² values can range between 0 and 100%; 0% indicates no observed heterogeneity; larger values indicate increasing heterogeneity. Subgroup analyses were used to explore the reasons for heterogeneity. Publication bias was assessed using a funnel plot and Egger’s statistical test (25, 26). All statistical analyses were performed using StatsDirect Software (2002, Cheshire, UK).

RESULTS

Study selection

The database search retrieved 38 citations of which four met our inclusion criteria (Fig. 1) (17-20) Manual search identified one trial presented in abstract form during an American Society of Clinical Oncology meeting which met the inclusion criteria (27). The remaining studies fell into one or more of the following exclusionary categories: non-randomized trials of prophylaxis or any trials of urokinase as adjunctive therapy of IVD-associated BSI (n=30) and review articles (n=4). All studies were in the English language.

Study characteristics

The trials enrolled 991, of which 953 were included in the analysis; 484 patients received a urokinase-heparin lock or flush solution and 469 patients received heparin alone. All five trials included patients with hematologic malignancy. Two studies included
only subcutaneous ports (18, 27), one included both tunneled CVCs and subcutaneous ports (20) and the remaining two included only tunneled IVDs. The characteristics of the five randomized controlled trials are summarized in Table I. Routine catheter care varied among the included studies and were not explicitly stated in any of the included trials. In the Children’s Oncology Study Group individual institutional practices for catheter care and heparin flushing were permitted (20).

Details of randomization

Block randomization was used in one trial (18). Ray et al used a computer-driven random number generator (17). Details of randomization were not provided for the other three studies. Only one study was conducted in a double-blind manner (18). The study by Solomon et al was the only study to report an intention to treat analysis (19).

Definition of BSI

The diagnostic criteria used for BSIs in the included trials were as follows: Positive blood culture drawn from the catheter with no other site of infection; or if a culture could not be drawn from the catheter, removal of all signs and symptoms of infection following catheter removal and a positive tip culture or a positive peripheral blood culture with no other site of infection (20). Fraschini et al (27) defined catheter-associated BSI as a positive blood culture from the catheter with or without a positive peripheral blood culture with no other site of infection. Solomon et al defined catheter-associated BSI as the development of fever and bacteremia or fungemia in a patient with a uninfamed Hickman catheter in whom fever and bacteremia resolve upon removal of the catheter within 48 hr (19). Ray et al used a positive catheter tip culture for diagnosis of bacteremia (17). The study by Aquino et al included all bacteremias as part of their definition of catheter related bacteremia (18).

Studies used either lock solutions or flush solutions. We considered solutions to be lock solutions if they were allowed to dwell in the lumen of the IVD for a prescribed period of time and if the device was not immediately used for parenteral infusion. Of the studies that used this criteria, Ray et al and Solomon et al evaluated a urokinase-heparin lock solution (17, 19). Fraschini et al evaluated locking of either urokinase or heparin though the duration of locking was not provided (27). Aquino et al and Dillon et al, evaluated urokinase-heparin flush solutions (18, 20).

Effect of urokinase on thrombosis

Three trials reported data on the efficacy of urokinase for prevention of catheter occlusion or thrombosis. Fraschini et al found that catheter occlusion was less frequent in the urokinase group but the results were not statistically significant (27). Ray et al found a significantly reduced incidence of catheter occlusion in their study (17). In contrast, Solomon et al found no difference in venous thrombosis or catheter occlusion in their trial, where urokinase was used twice weekly for approximately 8 weeks (19). However, in this study, only clinically evident occlusion or thrombosis was evaluated. Dillon et al and Aquino et al did not report data on catheter occlusion or venous thrombosis (18, 20).

Incidence of IVD-associated BSI

Table I shows the incidence of IVD-associated BSI in the included trials. In three studies, urokinase was associated with a decrease in IVD-associated BSI (17, 20, 27), while two trials found no difference in rates of IVD-associated BSI in the patient population under study (18, 19).

Overall, 87/953 or 9% of patients developed IVD-associated BSI in the treatment group compared with 114/953 or 12% of patients in the comparator group. The Mantel-Haenszel pooled estimate of relative risk was 0.74 (0.58-0.94) (Fig. 2), indicating a beneficial effect of urokinase instillation for prevention of BSI. Using the random effects model, the DerSimonian-Laird pooled relative risk was 0.77 (95% CI 0.60-0.98), p=0.01.
Urokinase to prevent bloodstream infection

| Author, year | Patient population | Types of devices | Urokinase-heparin instillation regimen | Duration of implantation
days | No. of catheters/patients | No. of BSI | Rate of BSI * |
<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Aquino et al, (18)</td>
<td>Children with cancer</td>
<td>Subcutaneous port</td>
<td>Monthly flushing of 5000 IU</td>
<td>348</td>
<td>332</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Dillon et al, (20)</td>
<td>Children with cancer</td>
<td>Tunneled CVCs and subcutaneous ports</td>
<td>Every 2 weeks 5000 IU urokinase</td>
<td>NR</td>
<td>NR</td>
<td>284</td>
<td>284</td>
</tr>
<tr>
<td>Ray et al, (17)</td>
<td>Adults requiring radiologic placement of tunneled device</td>
<td>Tunneled CVCs</td>
<td>Twice-daily heparin and once weekly UK 9000 IU</td>
<td>99</td>
<td>104</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Solomon et al, (19)</td>
<td>Hematologic malignancy</td>
<td>Tunneled CVCs</td>
<td>5000 IU urokinase twice weekly</td>
<td>NR</td>
<td>NR</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>Fraschini et al, (27)</td>
<td>Patients with cancer</td>
<td>Subcutaneous ports</td>
<td>5000 IU urokinase at 3-4 week intervals</td>
<td>104</td>
<td>98</td>
<td>55</td>
<td>51</td>
</tr>
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</table>

* per 1000 catheter-days; *days, mean

(Fig. 3). Only a single study reported the rate of IVD-related BSI using patient-days as a denominator and we were unable to calculate a combined rate ratio.

Publication bias

Given the small number of studies that met our inclusion criteria, publication bias was of concern and was found to be present. We undertook an exhaustive search to identify additional unpublished studies and did not identify any other trials that met inclusion criteria.

Assessment of heterogeneity

There was substantial clinical heterogeneity in the included studies with differing patient populations, although most included patients had cancer, concentration and frequency of instillation of urokinase, and definition of IVD-associated BSI. Using the Q statistic, we did not find statistical heterogeneity (p=0.53) and an alternate test for heterogeneity, I² was 0% (95% CI 0-64%) indicating no heterogeneity.

Cost of urokinase

Only a single study estimated the cost of urokinase (17). Ray et al found that addition of daily prophylactic urokinase added $3,398 per patient. No formal cost-effectiveness analysis was undertaken in any study.

Adverse effects of urokinase

In three of the five studies included in our analysis, no adverse consequences of urokinase, such as bleeding complications, were noted (17, 18, 20). Solomon et al reported adverse events in 38 patients receiving urokinase (19). However, most were related to chemotherapy being received or underlying disease...
and none could be attributed to urokinase. Fraschini et al did not report adverse effects in their abstract (27).

DISCUSSION

Prevention of bloodstream infections in patients with IVDs is essential. In recent years, several randomized trials have been undertaken to identify efficacious strategies for prevention of IVD-related BSI (28-30). Many have focused on cutaneous antisepsis (29) and most have included patients with short-term devices, where the extraluminal route of infection is most common (31). For long-term devices, where most infections occur by the intraluminal route, use of anti-infective lock solutions has been found to prevent BSI (32). However, the most widely studied lock solution has been vancomycin and concerns have been raised that this novel form of local antimicrobial prophylaxis will promote resistance. It remains important to explore other avenues for prevention of IVD-associated BSI.

Previous studies have shown a close association between CVC-related infection with thrombosis (13-16, 33). Urokinase, a thrombolytic agent previously derived from human kidney cells, is a protein enzyme which acts on the endogenous fibrinolytic system (34). It converts plasminogen present in clots to plasmin which subsequently degrades fibrin clots. Initially approved by the FDA in 1978, urokinase was held off the market in 1999 for manufacturing violations. The FDA has reapproved a new formulation of urokinase for the treatment of pulmonary embolism in October 2002. Several studies of urokinase and IVDs have focused on urokinase as adjunctive treatment of IVD-associated BSI with mixed results (35-39). Prospective trials evaluating various dose regimens of urokinase in restoring catheter patency have found urokinase both to be safe and efficacious in removing occlusion (40-44). However, urokinase for the prevention of IVD-associated BSI in patients receiving chemotherapy has found conflicting results.

Our analysis of five prospective, randomized trials shows a 25% reduction in the relative risk for IVD-associated BSI with the use of a urokinase-heparin lock or flush solution. There are no recommendations regarding use of urokinase for prevention of IVD-associated BSI in the 2002 Centers for Disease Control and Health Care Infection Control Practices Advisory Committee (HICPAC) (45). Given the overall small sample size, despite our inclusion of all the available literature, a large randomized trial is necessary to determine the role of urokinase for the prevention of IVD-associated BSI. Future studies should...
endeavor to identify optimum doses and regimens of urokinase to maximize efficacy and reduce cost and adverse effects.

Our meta-analysis has several limitations. First, the studies were clinically heterogenous with regards to patient populations (pediatric vs. adult), although all included patients with cancer. Secondly, several of the studies included small sample sizes whereas the Children's Oncology Group Study, which found a significant benefit, had the largest sample size of all the studies (20). This discrepancy in sample size could potentially overshadow results of the smaller trials contributing to Type 1 error. Finally these studies were conducted with the previous formulation of urokinase prior to FDA withdrawal. Now urokinase is developed from human neonatal cells grown in tissue culture. Recombinant urokinase developed from non-human mammalian cells is currently under study. Future studies with larger sample sizes involving these new formulations will be needed in the future.

In conclusion, we found that urokinase-heparin used in ascheduled lock or flush protocol can substantially reduce the risk of bacteremia in patients with long-term IVDs. Consideration should be given to the use of a urokinase lock for preventing bacteremia in high-risk, vulnerable patients. Further research is necessary to determine the optimal dose and schedule to maximize efficacy and reduce likelihood of adverse effects.

Conflict of interest statement: The authors have no financial interests to disclose.

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