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Lack of efficacy of twice-weekly urokinase in the prevention of complications associated with Hickman catheters: a multicentre randomised comparison of urokinase versus heparin

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Abstract

Hickman catheters (HC) are associated with complications, in particular infection, occlusion and thrombosis. We tested the hypothesis that regular flushing of catheters with urokinase would reduce the frequency of these complications. Patients who required a double-lumen HC for (1) bone marrow or peripheral blood progenitor cell transplantation or (2) intensive combination chemotherapy for haematological malignancies were randomised to receive twice-weekly flushes of either urokinase (5000 units) or heparin (50 units). HC-survival analysis was determined by Cox regression. 100 patients were enrolled (urokinase = 52; heparin = 48) and treated for a mean of 8.5 weeks. No significant difference was observed in the incidence of HC-associated septicaemic events, which occurred in 8/52 in the urokinase group and 9/48 in the heparin group (actuarial incidence 20% versus 25%, $P = 0.50$). Similarly, there was no differences in the incidence of exit site infections (urokinase = 27/52 and heparin = 28/48, $P = 0.122$); HC-septic thromboses (urokinase = 2/52 and heparin = 4/48, $P = 0.34$); lumen occlusion (urokinase = 30/52 and heparin = 30/48, $P = 0.681$); or venous thrombosis (urokinase = 8/52 and heparin = 6/48, $P = 0.726$). Overall, a high incidence of HC-related complications was seen in both groups; 40/52 in the urokinase group and 40/48 in the heparin group (actuarial incidence 80% versus 90%, $P = 0.367$). Despite this only 18% of HC required early removal due to complications (urokinase = 8, heparin = 10). There was no difference in the incidence of complications in patients undergoing transplantation ($n = 68$) compared with chemotherapy alone ($n = 32$). Patients with haematological malignancies were more likely to have HC-related infective complications ($P = 0.006$), and patients with solid tumours more likely to have venous thrombosis ($P = 0.027$). The cumulative incidence of HC-related complications in this prospective study was higher than in previously reported series. Urokinase did not appear effective in reducing the frequency of these complications.

Keywords: Hickman catheter; Urokinase; Heparin; Infection; Thrombosis

1. Introduction

Despite their convenience, Hickman catheters (HC) are associated with complications that can result in substantial morbidity. Previous studies have demonstrated that the most frequent HC-related complications are infection and venous thrombosis, which result in premature catheter removal in 18–32% of cases [1–3]. Other complications include luminal occlusion, fracture, migration or dislodgment of the catheter. Given the morbidity associated with these events, it is important to explore means to reduce the frequency of HC-related complications.

Intraluminal catheter thrombosis has been associated with HC-related infection. Press and colleagues [4] in a study of 102 patients with HCs reported that five of six thrombosed catheters were associated with infections, whereas only 10 infections occurred in the remaining 123 non-thrombosed catheters ($P = 0.001$, relative risk 10.2). One hypothesis to explain this association is that intraluminal fibrin or thrombus acts as a matrix for the adherence of bacteria, facilitating colonisation and ultimately overt infection. Consequently, in an attempt to reduce fibrin/thrombus formation many centres routinely 'flush' and 'lock' catheters with heparin or heparinised saline. However, although heparin will prevent

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thrombus formation while it is in contact with the catheter, it will not dissolve an existing thrombus. In contrast, fibrinolytic agents are capable of lysing fibrin/thrombus deposits, which potentially may reduce the frequency of subsequent infection.

Urokinase is one such thrombolytic agent and has frequently been used to restore the patency of occluded Hickman catheters [5]. Frashini and colleagues in 1991 reported, in abstract form, that regular urokinase flushes reduced the frequency of infections in implanted subcutaneous ports [6]; 106 patients were randomised to receive flushes with either urokinase or heparin, with a significantly lower infection rate in the urokinase group (1.8% versus 14%, $P=0.03$). In this study, we examined the hypothesis that the regular instillation of urokinase into double-lumen Hickman catheters would be superior to heparinised saline in reducing HC-related complications.

2. Patients and methods

The study was a prospective open-label, randomised controlled trial comparing a twice-weekly catheter 'lock' using urokinase, with a twice-weekly lock using heparinised saline for the prevention of complications associated with double-lumen Hickman catheters. It was conducted at two centres (Peter MacCallum Cancer Institute and Royal North Shore Hospital) over a 12-month period. The study was approved by the respective institutional ethics committees and all patients provided written informed consent.

2.1. Patients and eligibility

Patients who required a double-lumen HC for either (1) autologous or allogeneic bone marrow/peripheral blood progenitor cell transplantation or (2) intensive combination chemotherapy for the treatment of acute leukaemia, lymphoma, myeloma or myelodysplastic syndrome were included in this study. This had to be the first catheter placed for the episode of treatment with a projected placement time of at least 6 weeks (transplant group) or 13 weeks (chemotherapy group). All patients were over 16 years of age. Patients were excluded from the study if they were taking oral anticoagulants or if there were contraindications to low dose thrombolytic therapy or low dose heparin (including a history of heparin-induced thrombocytopenia).

2.2. Randomisation

Randomisation occurred within 48 h of catheter placement, at a central location (Serono Australia, Sydney). Stratification was by planned treatment regimen, i.e. patients undergoing (1) transplant or (2) intensive chemotherapy alone.

2.3. Treatment

Patients were randomised to receive either urokinase (5000 units in 2 ml normal saline, Ukidan®, Serono laboratories, Sydney, Australia) or heparin (50 units in 5 ml normal saline) instilled in both lumens of their HC, twice weekly. The urokinase was supplied in ampoules containing 5000 units of freeze dried urokinase and was stored below 25 °C until it was reconstituted with 2 ml sterile saline prior to use. Commercially available unfractionated heparin prepared as ampoules of 50 units in 5 ml of normal saline were used. The first dose of the study medication was administered within 48 h of catheter placement.

Locking of the HC was performed twice weekly. To ensure uniformity, there was strict adherence to this twice-weekly lock regimen. If the lumen was not in use at the time of planned locking, the study drug was instilled and left in the catheter until the next time it was accessed. If a continuous infusion was ongoing at the time of planned lock, it was ceased temporarily, the HC flushed with saline, and study drug instilled and left in the catheter for 1 h, after which the infusion was resumed.

The locking was performed twice weekly by hospital or community nurses and routinely documented on data collection forms. Patients were assessed on an ongoing basis for evidence of HC-related complications.

2.4. Definitions of events

Infective complications were defined as described by Press and colleagues [4] namely, *Exit site infections:* the development of pain, tenderness, inflammation or purulent exudate within 2 cm of the exit site; *Tunnel infections:* the development of pain or erythema along the subcutaneous course of the catheter more than 2 cm from the exit site; *HC-related septicaemia:* the development of fever and bacteraemia or fungaemia in a patient with an uninflamed HC tract in whom fever and bacteraemia resolve upon removal of the catheter within 48 h; and *HC-related septic thrombophlebitis:* the development of a venous occlusion in proximity to the HC associated with bacteraemia and fever. HC-related venous thrombosis was defined as clinically evident, ultrasonographically-confirmed, venous thrombosis in the region of the catheter.

2.5. Statistical analysis

The primary endpoint of the study was the incidence of microbiologically confirmed, HC-related septicaemic infections. The secondary endpoints included other infections, catheter occlusions, HC-related venous thrombosis, and all combined HC-related complications. A separate analysis was prospectively planned to compare the above endpoints by treatment group undergoing transplant compared with chemotherapy alone. HC-survival analysis was assessed by Cox regression. This method took account of the period that

the HC was in place and the stratification by centre, underlying disease and method of treatment for disease (transplantation versus chemotherapy). The analysis of all efficacy endpoints was on an intention-to-treat basis, including all patients who had a HC inserted and who were randomised.

3. Results

3.1. Patient characteristics

One hundred patients were enrolled into the study, and randomised to receive heparin ($n=48$) or urokinase ($n=52$). The characteristics of the patients were well matched (Table 1). The majority of patients underwent transplantation (67% heparin, 69% urokinase) mainly with autologous peripheral blood progenitor cells. The female preponderance (63% heparin, 71% urokinase) was a consequence of women undergoing autologous transplantation for breast cancer.

The mean duration of treatment was 8.5 weeks (8.2 weeks (range: 2–13 weeks) for the heparin group and 8.8 weeks (range: 2–13 weeks) for the urokinase group). Withdrawal from the study prior to the projected duration of study drug treatment occurred in 17 (35%) patients in the heparin group and in 20 (38%) from the urokinase group (Fig. 1); this included 7 patients who had their HC removed electively as they were no longer required and 14 who had catheters removed as a result of non-catheter related complications. Seven patients in each treatment group were withdrawn because of adverse events relating to their disease treatment. Two patients died in each group and four catheters were accidentally dislodged (heparin = 3, urokinase = 1). One patient was transferred to another hospital (heparin group). All patients were included in the analysis.

Of the twice-weekly treatments, the incorrect drug was given on 32 occasions (of 1700 treatments); in 28 of these heparin was given instead of urokinase, in two saline was given instead of heparin and on a single occasion urokinase was given instead of heparin. Interruptions

Table 1
Patient characteristics

	Total	
	Heparin $n=48$	Urokinase $n=52$
Age (years)		
n	48	52
Mean	46.37	51.63
Sex		
Male	18 (38%)	15 (29%)
Female	30 (63%)	37 (71%)
Race		
Caucasian	47 (98%)	51 (98%)
Underlying condition		
Leukaemia	7 (15%)	7 (13%)
de novo	5	5
Relapsed/refractory	2	2
Myeloma	6 (13%)	5 (10%)
Breast cancer	17 (35%)	19 (37%)
Lymphoma	11 (23%)	14 (27%)
Ovarian cancer	5 (10%)	4 (8%)
Other	2 (4%)	3 (6%)
Treatment for underlying condition		
Combination chemotherapy	16 (33%)	16 (31%)
Autologous bone marrow transplant	4 (8%)	7 (13%)
Allogeneic bone marrow transplant	1 (2%)	0
Peripheral stem cell transplant	27 (56%)	29 (56%)
Catheter details		
Right side insertion	35 (73%)	39 (75%)
Left side insertion	13 (27%)	13 (25%)
Inserted by		
Surgeon	36 (75%)	39 (75%)
Radiologist	12 (25%)	13 (25%)
Entrance site		
Sub-clavian	46 (96%)	51 (98%)
Jugular	2 (4%)	1 (2%)

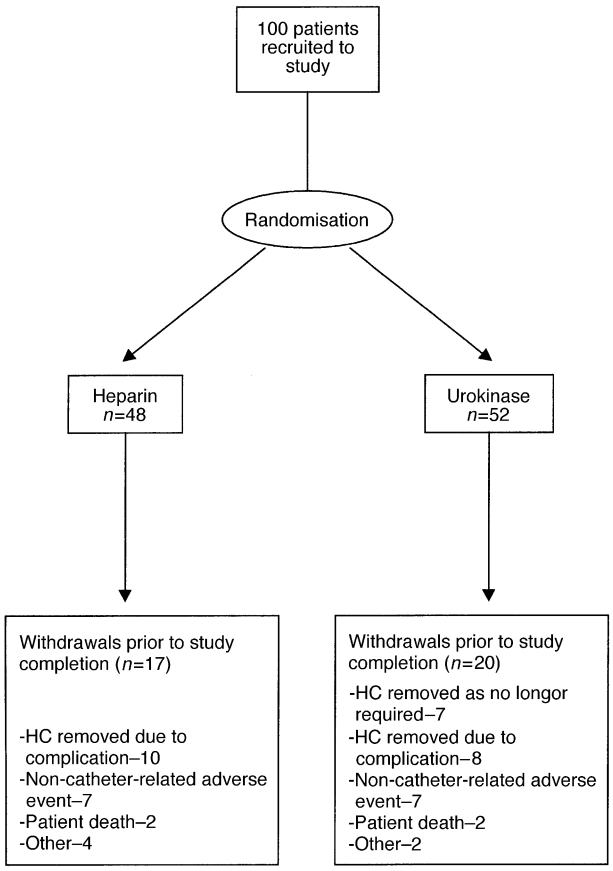

Fig. 1. Randomisation of patients to heparin and urokinase, and details of patient withdrawal from study. Withdrawal was defined as a patient having less than 6 weeks treatment in the transplant or less than 13 weeks in the chemotherapy group. 12 patients reported two reasons for withdrawal.

to treatment were very infrequent and of short duration (data not presented).

3.2. HC-related complications

- *HC-related septicaemic infections* were confirmed in 9/48 patients in the heparin group and 8/52 patients in the urokinase group. In the Kaplan–Meier analysis, the actuarial incidence of HC-related septicaemic infection was 25 and 20%, respectively (Fig. 2), with no significant difference between the two treatment groups ($P=0.50$).
- *Other HC-related infections*: The majority of infections observed during the study were HC exit site infections. These were recorded in 28 patients in the heparin group and 27 in the urokinase group. In the Kaplan–Meier analysis, the actuarial incidence of infection was 68 and 59%, respectively ($P=0.122$).

  HC-related septic thromboses were observed in 4 patients in the heparin group and two in the urokinase group ($P=0.34$). Hickman catheter tunnel infections occurred in 2 patients in the heparin group and 4 in the urokinase group ($P=0.507$).

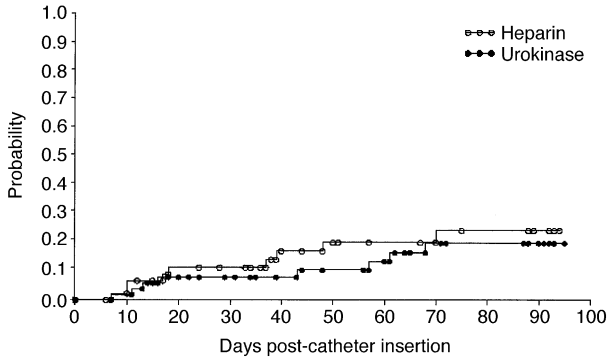

Fig. 2. Kaplan–Meier estimate of incidence of Hickman-catheter-related septicaemic infections in the heparin and urokinase groups ($P=0.50$).

Overall, 31 patients in each treatment group recorded at least one HC-related infection, with no significant difference between the two treatment groups ($P=0.117$). Similarly, when all infections (catheter-related or otherwise) were examined, the actuarial rate of infection was not significantly different between groups (90% for heparin and 89% for urokinase).

- *Venous thromboembolism*: There were 6 patients in the heparin group and eight in urokinase with Hickman catheter-related venous thrombosis during the course of the study. In the Kaplan–Meier analysis, the actuarial incidence of venous thrombosis was 16 and 19%, respectively, and by Cox regression analysis there was no significant difference in the incidence of HC-related venous thrombosis between the two treatment groups ($P=0.726$). Patients with solid tumours were more likely to experience HC-related venous thrombosis than those with haematological malignancies ($P=0.027$). In most instances (12 of 14), the HC-related thrombosis was managed by removal of the catheter and therefore withdrawal from the study. 7 patients commenced oral anticoagulation (2 heparin; 5 urokinase). One patient had a pulmonary embolus.
- *Lumen occlusion*: 30 patients in each treatment group recorded at least one HC lumen occlusion and in the Kaplan–Meier analysis of time to the first lumen occlusion, the actuarial incidence of occlusion was 74% in the heparin group and 63% in the urokinase group. In the Cox regression analysis, there was no significant difference in the incidence of lumen occlusion between the two treatment groups ($P=0.681$), and no other factors were significant in the model.

3.3. Catheter survival

Hickman catheter survival was calculated as the time from catheter insertion to removal, or to the date of the last study medication plus 4 days. All catheters were removed by day 95 post-catheter insertion. There was no difference between the treatment groups in catheter survival time ($P = 0.963$), and no other factors were significant in the Cox regression model. Of note, only 18% of HC (heparin = 10, urokinase = 8) were removed early due to complications.

Despite the low rate of removal of catheters, there was a high rate of catheter complications. Using the end-point of 'any HC-related complication', events occurred in 40/48 patients in the heparin group and 40/52 in the urokinase group (Fig. 3). This difference was not statistically significant ($P = 0.367$). Indeed, within two weeks of HC insertion approximately 50% of patients in both groups developed one or more HC-related complications.

There was no significant difference in any of the regression models for the treatment method, comparing transplantation ($n = 68$) and chemotherapy alone ($n = 32$), with respect to any of the complications listed above. However, patients with haematological malignancies were more likely to have infective complications ($P = 0.006$) and patients with solid tumours more likely to have venous thrombosis ($P = 0.027$) on multivariate Cox regression analysis.

3.4. Safety

Adverse events were recorded up to 30 days after the removal of the catheter. Almost all patients (98%) in both treatment groups reported adverse events, including serious adverse events in 32 patients in the heparin group compared with 38 in the urokinase group. Most adverse events related to the underlying condition or chemotherapy the patients were receiving and none could be attributed to the heparin or urokinase.

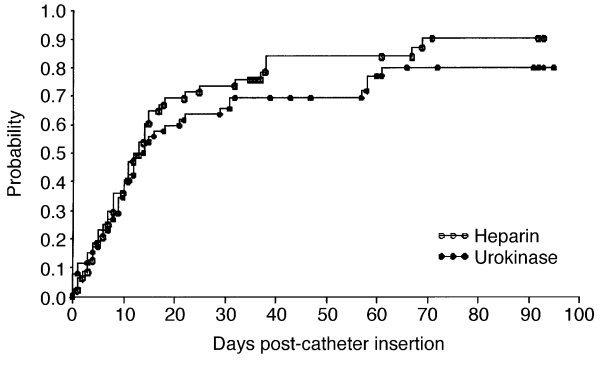

Fig. 3. Kaplan–Meier estimate of incidence of any Hickman-catheter-related complication in the heparin and urokinase groups ($P = 0.367$).

4. Discussion

The cumulative incidence of HC-related complications in this study was higher than in previously reported series [4,7,8]. The most common complication was exit site infection with an actuarial incidence of 68 and 59% in the heparin and urokinase groups, respectively. Furthermore, the risk of sepsis associated with HC catheters (20–25%) was substantial. The likely reason for the high reported complication rate is the prospective evaluation of complications with strict adherence to reporting occurrences of complications, including those that did not lead to the removal of the catheter. The intensity of the chemotherapy regimens used may be a further factor. Of note, the data were internally consistent across treatment groups and centres, indicating that the results were unlikely to be a result of the intervention, or the institution. Nonetheless, despite the high complication rate, only 18% of HC required premature removal.

The use of twice weekly urokinase was not effective in reducing the complications associated with double-lumen Hickman catheters. With respect to the primary endpoint of HC-related septicaemia, no statistically significant differences were observed between the urokinase (20%) and heparin (25%) groups. Similarly, other HC-related complications, including occlusion and thrombosis, occurred at very similar rates in both groups. There were no adverse events attributable to the urokinase.

The reported incidence of venous thrombosis (16–19%) is similar to other series [9] and was not influenced by the use of urokinase compared with heparin. Of note, low-dose warfarin, which has previously been demonstrated to reduce the incidence of thromboses [10,11], was not used because of the intensity of the chemotherapy and its associated risk of thrombocytopenia and liver dysfunction. The finding on multivariate analysis that patients with solid tumours were more likely to have venous thrombosis ($P = 0.027$) and patients with haematological malignancies were more likely to have infective complications ($P = 0.006$) is consistent with the findings of Anderson and colleagues [12] who found that thromboembolism was the major complication in patients with solid tumours.

In contrast to our findings, Ray and colleagues [13] recently reported a study of 105 patients demonstrating a benefit of once-weekly urokinase instillation added to twice-daily heparin flushes in reducing the combined endpoint of catheter occlusion and infection. The benefit, however, was confined to occlusion alone, and as in our study there was no difference in the infection rate, catheter-related venous thrombosis or catheter removal.

The reason for this apparent lack of efficacy of urokinase is unclear, but may be due to the administration of a urokinase dose insufficient to eradicate established

fibrin sheaths or thrombus. Supporting this possibility is a report by Montura and colleagues [14] who administered an identical dose of urokinase and were only able to restore patency in one-third of occluded catheters. In contrast, Haire and colleagues [15] were able to restore the patency in almost all occluded catheters when large doses of urokinase were used (5000 U bolus followed by a 12-h infusion of 40 000 U/h). However, while there may be a dose-response effect for urokinase, increasing the urokinase dose for prophylactic therapy is not practical because of the potential risk of bleeding. It is also likely that the model of fibrin as a nidus for bacteria is an oversimplification. Indeed, other factors, such as adhesion of bacteria to the internal-lumen of the catheter by means of biofilm production mediated by polysaccharide intercellular adhesin/haemagglutinin, may be of importance [16].

Given the high incidence of HC-related complications, in particular infection (59–68%), other methods to reduce these complications warrant further investigation. These include the instillation of antibiotics [17] or the use of antibiotic-impregnated catheters [18]. Unfortunately, both interventions have the potential risk of inducing antibiotic resistance.

In summary, a higher than expected cumulative incidence of HC-related complications was observed, with up to quarter of patients experiencing HC-related septicaemia. However, twice-weekly instillation of urokinase did not result in a reduction in HC-septicaemia or other complications, including occlusion and thrombosis, compared with heparin instillation. Thrombolytic agents such as urokinase cannot be recommended for routine use in the prevention of complications of Hickman catheters.

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