ORIGINAL ARTICLE

Antibiotic lock solutions for the prevention of catheter-related bacteraemia in haemodialysis patients

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Objective To investigate the effect of antibiotic lock solutions for preventing catheter-related bacteraemia in patients receiving haemodialysis.

Design Retrospective study.

Setting University teaching hospital, Hong Kong.

Patients Consecutive patients from March 2006 to April 2007 who had central venous catheter insertion for haemodialysis in our centre were included in this historically controlled study. In all, 75 patients had catheters with heparin solution alone and 74 had catheters with a gentamicin antibiotic lock. The majority of catheters were non-tunnelled (95%). Cumulative catheter survival free of catheter-related bacteraemia in the two groups was compared.

Results Baseline characteristics in the two groups were similar apart from a slightly lower serum albumin level in those with gentamicin locks. There were 18 and five catheter-related bacteraemia episodes before and after recourse to gentamicin antibiotic locks, respectively. *Staphylococcus aureus* contributed to over half (65%) of the total bacteraemia episodes. Use of gentamicin antibiotic locks significantly reduced catheter-related bacteraemia episodes per 1000 catheter days from 4.6 to 1.5 (P=0.002). Kaplan-Meier survival analysis using the log rank test showed significantly better bloodstream infection–free survival associated with using gentamicin antibiotic locks (P=0.032). A similar survival advantage was associated with gentamicin antibiotic locks when the analysis was restricted to non-tunnelled catheters. There was no significant association of catheter-related bacteraemia with patient age, obesity, gender, baseline serum albumin level, or diabetes mellitus. No serious adverse events were attributable to the use of gentamicin antibiotic locks.

Conclusion Use of gentamicin lock solutions effectively reduced catheter-related bacteraemia in haemodialysis patients, including those with non-tunnelled catheters.

Key words
Anti-infective agents; Bacteremia; Catheters, indwelling; Infection control; Renal dialysis

Hong Kong Med J 2010;16:269-74

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Introduction

Catheter-related bloodstream infection remains a major cause for the catheter loss, and has been associated with significant morbidity and mortality among haemodialysis patients.[1] Because microorganism biofilm matrix formation on the internal surface of vascular catheters is now thought to be a crucial mechanism responsible for catheter-related bacteraemia, instilling an antimicrobial solution into the lumen represents a logical preventive strategy.

Although catheter lock solutions for the purpose of preventing infection have not been recommended in the Kidney Disease Outcomes Quality Initiative guidelines[2] and the Centers for Disease Control and Prevention guidelines,[3] accumulating evidence shows the practice to be beneficial.[4] Three recent meta-analyses have demonstrated that recourse to intraluminal antibiotic lock solutions reduces the rate of catheter-related bacteraemia by 56 to 68%.[5-7] The number needed to treat to prevent one catheter-related bloodstream infection per 100 catheter days was three (patients).[7]

血液透析病人使用抗生素封存液以防止因透析導管感染引起的菌血症

目的 探討使用抗生素封存液防止血液透析病人中因透析導管感染引致菌血症的效果。

設計 回顧研究。

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患者 本歷史對照研究包括所有於2006年3月至2007年4月，前往上述醫院透過中央靜脈透析導管進行血液透析的病人。其中75位病人的透析導管只有肝素液，另74位的透析導管則加有慶大霉素的抗生素封存液。大部份（95%）透析導管屬於無管路。研究把兩組病人與透析導管有關的菌血症的陰性結果作比較。

結果 除了封存液組的病人有稍低的血清蛋白水平外，兩組病人的基線特徵相似。施行慶大霉素的抗生素封存液前，有18宗與透析導管有關的菌血症；而使用抗生素封存液後，只有5宗。金黃色葡萄球菌出現在一半以上（65%）的菌血症病例。慶大霉素抗生素封存液明顯減少因透析導管感染引致的菌血症，由4.6/1000導管日降至1.5/1000導管日（P=0.002）。Kaplan-Meier存活分析與log rank test分析顯示慶大霉素抗生素封存液顯著改善無血流感染存活率（P=0.032）。只集中在無管路透析導管時的分析亦有類似的較佳存活率。與透析導管有關的菌血症證實與下列因素無關：病人年齡、肥胖、性別、基線血清蛋白水平和糖尿病。並未發現任何與慶大霉素抗生素封存液有關的嚴重不良事件。

結論 血液透析病人中，用慶大霉素的抗生素封存液能有效減少與包括無管路透析導管有關的菌血症。

The aim of this historically controlled trial was to investigate the impact of antibiotic lock solutions on preventing catheter-related bacteraemia among patients receiving haemodialysis. We hypothesised that use of antibiotic lock solutions in haemodialysis catheters, which became routine in our institution since 2007, would have reduced the rate of catheter-related bacteraemia. Using a retrospective chart review protocol design, the infection-free outcomes associated with haemodialysis catheters before and after introduction of antibiotic lock solutions were compared. Because most of the published data on antibiotic lock solutions referred to patients with tunnelled cuffed catheters, we were able to evaluate this strategy in a unit that predominantly used uncuffed catheters.

Methods

Case selection

We reviewed the records of all consecutive patients having central venous catheters inserted for haemodialysis at our centre. Both standard non-tunnelled and tunnelled cuffed catheters were used as vascular access during the study period, although the former were used preferentially in our institution. Catheter care protocols conformed to standard guidelines for haemodialysis vascular access.[8] This included catheter insertion using strict asepsis (sterile long-sleeved gowns, caps, masks, and large sterile drapes) and application of povidone-iodine ointment at the catheter exit site; the right internal jugular vein was used whenever possible. During dialysis, haemodialysis catheters were handled only by trained dialysis staff wearing masks and sterile gloves, undertaking no other intervention between treatments. Catheters were not used for routine blood sampling or drug administration. To minimise the risk of contamination during haemodialysis, the vascular catheter hubs were removed in a strictly sterile manner, with immediate connection to reduce exposure to air. The exit site was cleaned, and after each dialysis session a povidone-iodine impregnated dressing was applied.

Group of catheters with heparin solution alone

During the period March 2006 to April 2007, no antibiotic lock solution was used for locking the catheter lumen in our dialysis unit. At the end of each haemodialysis session, each port of the catheter was filled with 5000 U/mL of unfractionated heparin solution according to the volume of the ports.

Group of catheters with gentamicin antibiotic lock

Between the period May 2007 and November 2007, dialysis catheter lumens were routinely locked with gentamicin in addition to heparin at 5000 U/mL. The final concentration of gentamicin in the antibiotic lock solution was 5 mg/mL. Upon completion of each dialysis session, all the gentamicin-heparin locks were instilled into both lumens of the dialysis catheter, and withdrawn immediately prior to the next dialysis session.

Apart from the introduction of gentamicin lock solution, the protocol for central venous catheter insertion and care remained the same throughout the two periods. No concomitant nasal mupirocin was used during that period.

Clinical follow-up

All patients were followed up for 3 years. The definitive clinical outcome was bloodstream infection-free catheter survival. Catheter-related bacteraemias were defined as infections with the isolation of the same organism in blood cultures drawn from the peripheral blood and catheter, and

TABLE 1. Comparison of baseline characteristics between the two treatment groups*

Baseline characteristics	Catheters with heparin solution alone	Catheters with gentamicin antibiotic lock	P value
No. of dialysis catheters	75	74	-
Gender (male:female)	36:39	42:32	0.33
Age (years)	58 ± 14	59 ± 13	0.62
Duration of dialysis (years)	4 (2-7)	4 (1-6)	0.38
Body mass index (kg/m^2)	23 ± 4	24 ± 4	0.08
Percentage of patients with diabetes mellitus	23%	34%	0.15
Serum albumin level during catheter insertion (g/L)	34 ± 7	30 ± 8	0.004
Site of catheter placement (internal jugular : subclavian : femoral)	61 : 4 : 10	66 : 0 : 8	0.12
Percentage of tunnelled cuffed catheters	5%	4%	1.00

* Data are shown as No. of patients, mean ± standard deviation, or median (interquartile range), unless otherwise specified

with no other cause for the infection.[9] Infection-free survival of a catheter was defined as the period between its insertion and the first positive blood culture obtained from that catheter. Blood cultures were obtained when catheter-related bacteraemia was clinically suspected. No surveillance blood cultures were undertaken during the study period. Censoring events for catheter survival analysis included removal of that catheter for malfunction, obstruction or poor blood flow, elective removal of the catheter (permanent vascular access ready to use), or end of study with a functioning catheter.

Data were extracted concerning the type and site of catheters, duration of follow-up, patient characteristics (including diabetes mellitus, age, body size, and baseline serum albumin concentration). Patients were also monitored clinically for any systemic adverse effect from antibiotic lock solutions; gentamicin levels were not checked.

Statistical analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 16.0; SPSS Inc, Chicago [IL], US). All data were expressed as mean ± standard deviation, unless otherwise specified. Data were compared by Chi squared test, Fisher's exact test, Student *t* test, or one-way analysis of variance, as appropriate. Survival analysis techniques were used to model infection-free catheter survival from the time of catheter insertion. Kaplan-Meier analysis and the log rank test were used to compare the cumulative infection-free catheter survival in patient groups. A P value of less than 0.05 was considered significant. All probabilities were two-tailed.

Results

During the 14-month interval from March 2006 to April 2007 (historical cohort period), a total of 75 patients had dialysis catheters inserted and monitored; they were locked with heparin alone without any antibiotic solution. From May 2007 to November 2007, we followed up 74 patients with dialysis catheters that were locked with gentamicin and heparin. The baseline clinical data related to the two catheter groups were similar, except for a slightly lower mean serum albumin level in the gentamicin lock group (Table 1). The mean age of patients was 58 years, and 28% of them had diabetes mellitus. The majority of catheters were non-tunnelled (95%) and were mainly situated in the jugular position (85%). A total of 7284 days at risk had accrued: 3944 days pertained to the historical cohort (heparin solution alone) and 3340 to the gentamicin antibiotic lock group.

TABLE 2. Bacteria isolated from the patients between the two treatment groups with catheter-related bloodstream infection

Bacteria isolated	No. of episodes of catheter-related bacteraemia	
	Catheters with heparin solution alone	Catheters with gentamicin antibiotic lock
Gram-positive bacteria	18/23 (78%)	4/23 (17%)
Staphylococcus aureus	12	3
Coagulase-negative staphylococci	6	1
Gram-negative bacteria	0/23 (0%)	1/23 (4%)
Escherichia coli	0	1
Total	**18/23 (78%)**	**5/23 (22%)**

We identified 23 episodes of catheter-related bacteraemia during the two periods. As listed in Table 2, the types of pathogens were predominantly Gram-positive microorganisms (95%). In particular, *Staphylococcus aureus* contributed to over half (65%) of all bacteraemia episodes. No yeasts were encountered. A total of 18 episodes occurred in the historical patient group given heparin solution alone, compared with five in the group with gentamicin

TABLE 3. Summary of the clinical data with reference to the events of catheter-related bacteraemia between the two treatment groups

Clinical data	Catheters with heparin solution alone	Catheters with gentamicin antibiotic lock	P value
Total No. of episodes of catheter-related bacteraemia	18	5	0.003
Catheter days (mean ± standard deviation)	53 ± 48	45 ± 37	0.29
Catheter-related bacteraemia episodes / 1000 catheter days	4.6	1.5	0.002

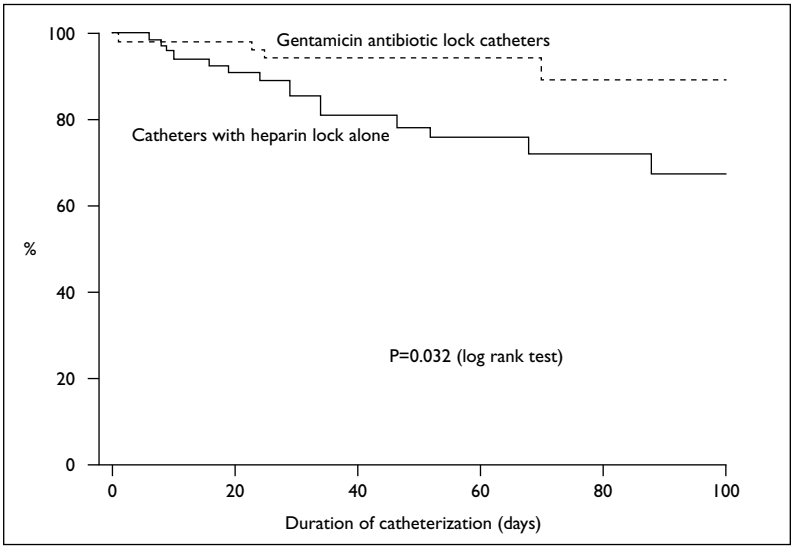

FIG 1. Kaplan-Meier cumulative survival curves demonstrating infection-free survival of catheters with and without gentamicin antibiotic locks

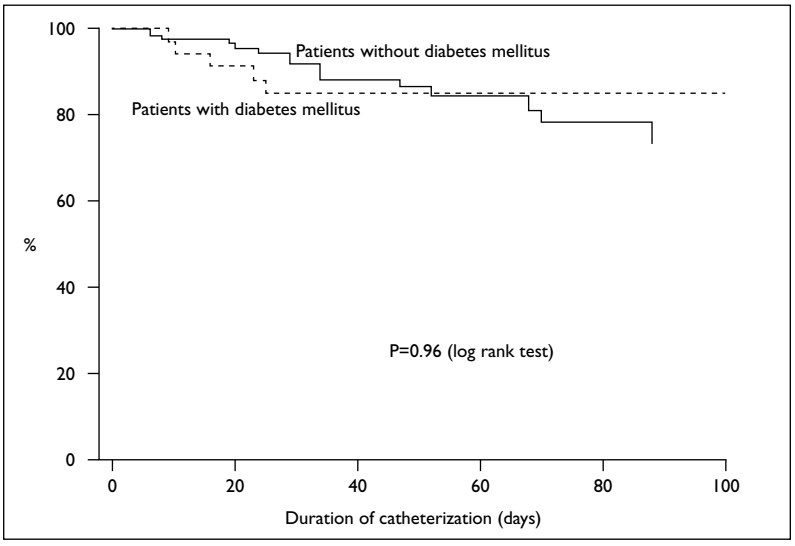

FIG 2. Kaplan-Meier cumulative survival curves of infection-free survival of catheters in patients with and without diabetes mellitus co-morbidity

antibiotic locks (P=0.003). In the latter group, catheter-related bacteraemia rates per 1000 catheter days were also significantly reduced; 4.6 in the historical group versus 1.5 for the gentamicin antibiotic lock group (P=0.002) [Table 3], and cumulative infection-free catheter survival (Fig 1) was significantly longer (log rank statistic, 4.60; P=0.032). Kaplan-Meier survival analysis, however, demonstrated no significant association of catheter-related bacteraemia with patient age, obesity, gender, baseline serum albumin level, obesity, and diabetes mellitus (Fig 2).

When the Kaplan-Meier analysis (Fig 3) was limited to non-tunnelled catheters, infection-free survival of the non-tunnelled catheters with gentamicin lock also remained significantly longer (log rank statistic, 5.48; P=0.019).

No patient death associated with catheter-related bacteraemia was noted during the study period. No serious adverse events (eg hearing loss) could be attributed to using antibiotic lock solutions. One instance of *Escherichia coli* bacteraemia occurred in the gentamicin antibiotic lock group and was resistant to gentamicin, and being an extended-spectrum-beta-lactamase (ESBL) producer, it was also resistant to cephalosporins. This patient had received eight courses of antibiotics within the previous 6 months. Such treatment included vancomycin, cotrimoxazole, ampicillin, cloxacillin, and amoxicillin-clavulanic acid, all of which are known risk factors for colonisation and infection by ESBL-producing organisms.

Discussion

This observational study adds evidence to the hypothesis that aminoglycoside antibiotic lock solutions represent an effective strategy to reduce the incidence of catheter-related bacteraemia, presumably by preventing lumen contamination and biofilm production. In particular, it supported the role of such locks even for indwelling non-tunnelled catheters, whereas previously published trials were mostly in patients with tunnelled cuffed (as opposed to uncuffed) catheters.[10-13]

Our study showed that gentamicin antibiotic locks improve the infection-free survival of dialysis catheters, and interestingly this survival advantage was also applicable to non-tunnelled catheters. The key to the success of antibiotic lock solutions appears to be their ability to attain intraluminal concentrations 100-fold in excess of the minimal inhibitory concentration, irrespective of whether tunnelled or non-tunnelled catheters are used. If biofilm formation is considered to be the major factor for catheter-related bacteraemia,[14,15] tunnelled

cuffed catheters might not offer any unique survival advantage. Risk of bacterial entry into the intraluminal catheter surface through a contaminated hub would be similar for tunnelled and non-tunnelled catheters, and results in the formation and attachment of a biofilm. In a recent meta-analysis of randomised controlled trials, the efficacy of antibiotic lock solutions as a means of reducing catheter-related bacteraemia was also shown to be unaffected by the proportion of catheters that were tunnelled.[16] On the basis of this meta-analysis and our findings, it is probably legitimate to assume that antibiotic lock solutions play an even more important role than catheter tunnelling in the prevention of catheter-related bacteraemia.

Although the present study was observational in nature (without randomisation), the historical control group was derived from the same dialysis population and had similar demographic and clinical characteristics (Table 1) as the gentamicin antibiotic lock group. If anything, patients in the latter group had lower baseline serum albumin concentrations, which has been shown to be an important risk factor for such bacteraemia in dialysis patients.[17] Achieving a catheter-related bacteraemia rate in the range of 1.5 episodes/1000 catheter days is currently the benchmark of a good standard for tunnelled catheters,[15] and lends further support to the role of gentamicin antibiotic locks. Furthermore, the recent finding of negative results with sodium citrate catheter locks[18] provides further justification for the use of antibiotic lock solutions.

These encouraging results from our study may have some limitations. First, the short follow-up period of our study did not allow us to detect the development of bacterial resistance possibly prevailing with more prolonged use. Second, we monitored neither random gentamicin blood levels nor clinical evidence of aminoglycoside ototoxicity in any systematic manner. Moreover, we cannot rule out possible spillage of solution into the systemic circulation, although the catheters were theoretically 'locked' (not over-filled) with gentamicin.[11,19] Notably, we used a much lower gentamicin concentration (5 mg/mL) than in another study[11] (27 mg/mL), in which there were some initial concerns about ototoxicity. Use of gentamicin lock solution at lower concentrations is thought to partly explain why thus far, no clinically evident ototoxicity has been reported in recent studies.[20]

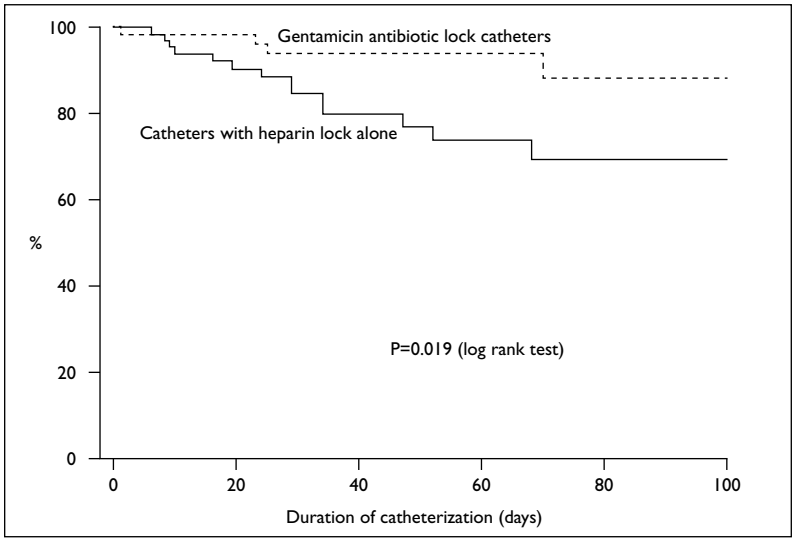

FIG 3. Kaplan-Meier cumulative survival curves of infection-free survival of non-tunnelled catheters with and without gentamicin antibiotic lock

In summary, data from the present study, combined with recently published randomised trials,[5,7,10,12,13] highlight the promising role of antibiotic lock solutions in preventing catheter-related bacteraemia among haemodialysis patients. Nevertheless, further evidence will need to show long-term safety before routine recommendation of this preventive strategy.

Acknowledgements

This study was supported in part by the Chinese University of Hong Kong research accounts. We thank Ms Shirley Sun-kiu Tsang for her clerical assistance.

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