

A NEW HAEMODIALYSIS CATHETER-LOCKING AGENT REDUCES INFECTIONS IN HAEMODIALYSIS PATIENTS

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SUMMARY

Background: Intravenous catheters for haemodialysis increase the risk of sepsis. This study investigates the use of a taurolidine/citrate catheter-locking agent for patients receiving hospital-based haemodialysis, auditing the number and cost of infections before and after its introduction.

Methods: The incidence and cost of treatment of catheter sepsis occurring in all patients receiving haemodialysis via a line were investigated over 6-month periods before and after introducing the taurolidine/citrate line-locking agent.

Results: A reduction of 4.62 infections per 1000 catheter days, or 88.5%, was shown after the introduction of the new line-locking agent.

The total costs of line infections in the first 6 months were €52 500, (£41 000); after the introduction of the taurolidine/citrate locks, these reduced to €33 300, (£26 000), a reduction of €19 200 (£15 000).

Conclusions: The use of a taurolidine/citrate haemodialysis catheter-locking agent in our haemodialysis population has significantly reduced the line sepsis rate, with a positive impact on morbidity, mortality and cost.

KEY WORDS Antibiotics • Haemodialysis • Hospitalisation • Infection • Intravenous catheter • Taurolidine-citrate

INTRODUCTION

All patients with established end-stage renal disease should receive dialysis using a high-quality access. This necessitates a timely and appropriate surgery for a permanent vascular access (Department of Health 2004). In the United Kingdom, only 37% of patients commencing haemodialysis in April 2006 did

so via a definitive access (UK Renal Registry Report 2006). Temporary access, via both tunnelled and nontunnelled dialysis catheters, is recognised to be associated with high levels of bacteraemia (Beathard G 1999; Saad 1999) and significant morbidity, mortality and healthcare expense. The risk of sepsis is higher in diabetes patients (Jean *et al.* 2004; Lee *et al.* 2004). The duration of catheterisation (Moro *et al.* 1994), use of urokinase (Pawar *et al.* 2004), immunosuppression with steroids (Nagashima *et al.* 2006) and a femoral site of catheter insertion (Haimi-Cohen *et al.* 2001) have also been reported to increase the risk of bacteraemia and sepsis. Gender and patient age do not appear to be associated with an increased risk.

A number of agents (as discussed by Mailloux *et al.* 1991; Kim *et al.* 2006) have been instilled into the catheters to try and reduce the catheter infection rates, but the results have been inconsistent, and the use of low concentrations of antibacterial agents has raised concerns over the development of bacterial resistance.

This study has looked at the infection rates, urokinase use, and cost incurred due to dialysis catheter infections before and after the introduction of a commercial taurolidine/citrate mixture (Taurolock®, Kimal Ag 2005) specifically designed for use in the lumens of intravenous catheters.

BIODATA

Caroline Taylor MSc MPharmS is a hospital pharmacist covering renal speciality wards, with 10 years of clinical experience working in a district general hospital. She is a member of the British Renal Pharmacy Group, EDTNA/ERCA and has presented at the British Renal Symposium and EDTNA/ERCA conference. She has an interest in ensuring the safety and efficacy of drugs prescribed to renal patients.



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SUBJECTS AND METHODS

HAEMODIALYSIS POPULATION

The Lincoln Haemodialysis Unit is part of the East Midlands Renal Network. Haemodialysis patients at the unit are drawn from a radius of 30 miles around Lincoln, a large town, in this area. All patients at the unit dialysing with a nondefinitive access (tunnelled catheters) were included in the study. This was a nonrandom selection of the subjects; the number of patients included in the study each month approximated 20. A written consent from all the subjects was obtained prior to the commencement of the study. The Trust Research and Development permission for the study was granted before the study began.

STUDY METHOD

The study ran for a total of 12 months. In the period between 1st June 2005 and 1st December 2005, the patients were managed in accordance with the standard network protocol. At the end of the dialysis session, an appropriate volume of 5000 units/ml preservative-free heparin was instilled into each lumen of the catheter. This was aspirated at the beginning of the next dialysis session. From 1st December 2005, an appropriate volume of the commercial taurolidine/citrate preparation was used in place of heparin. From 4th January 2006 onwards, due to an increase in the line flow problems, the commercial taurolidine/citrate preparation was mixed with 0.6 ml of preservative-free 5000 units/ml heparin prior to installation into the catheter lumens. This was done after consultation with the manufacturer. The mixture was aspirated prior to the next dialysis session.

Throughout the study, the patients with line flow problems were treated with urokinase instillations (12,500 units to each lumen for half an hour) or urokinase infusions (25,000–50,000 units to each lumen over 6 hours). The urokinase preparation used was the Synermed product imported from Italy.

The patients who developed a presumed haemodialysis catheter sepsis were treated according to the standard network protocol. This did not change during the study.

DATA COLLECTION

The patients' demographics of age, sex, diabetes mellitus status, data on immunosuppressive conditions (HIV, blood dyscrasias) and immunosuppressant drugs (including steroids) were collected from the renal unit database. Information on dialysis catheter survival (days), type and site of catheter and reason for change or removal of the dialysis catheter were collected prospectively.

All results from blood cultures taken on the dialysis unit were notified to the dialysis team by the microbiologists. Any positive culture in a patient with a dialysis catheter was regarded as an evidence of catheter-related bacteraemia. If patients had two positive cultures in less than 14 days apart, this was regarded as a relapse of an existing infection rather than a new infection, unless there was a change in the infecting organism. The time spent with a catheter infection was expressed as catheter days. Data on the infecting organism for each episode of sepsis were received from the microbiology department and documented on the study spreadsheet.

Data on in-patient days, X-rays for line replacement, numbers of new lines and antibiotic usage were collected and the relevant costs calculated using the standard tariffs. A cost comparison pre- and postintroduction of the agent was made that included the cost of purchasing the product. Data on urokinase usage and cost were collected throughout the study.

STATISTICAL ANALYSIS

The effect of the taurolidine/citrate preparation versus the standard heparin 'lock' on the number of days spent on the line sepsis protocol was characterised using a logistic regression. Catheters that crossed over on the 1st December 2005 and so were treated with both preparations were excluded.

A priori confounders considered in the analysis were age, site of dialysis catheter and diabetes mellitus status. Prior infection of the catheter, gender and high immunosuppressive risk (steroid use and HIV with lymphopaenia $<1 \times 10^9/l$) were tested as the potential confounders. The odds ratio was calculated for the incidence of line sepsis, adjusting for the main confounding factors by means of a multivariate logistic regression.

Data were tabulated using a Microsoft Excel Spreadsheet. The Pearson chi-squared test was applied to the data. A statistical analysis was carried out using a commercial statistics package—SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Twenty cross-over catheters were excluded from the analysis. After truncation of the pre-taurolidine/citrate period, there were 1802 catheter days in the pre-taurolidine/citrate group and 1669 in the taurolidine/citrate group. The group demographics are shown in Table 1. More diabetes patients were

	Standard catheter lock	Taurolidine/citrate catheter lock
Gender (% male)	65	60
Mean age, years (range)	65 (24–84)	59 (24–84)
No. of patients with diabetes	7	3
No. of patients with femoral site	3	3
No. of patients with immunosuppressive condition	2	2
No. of patients on steroids	2	1

Table 1: Group demographics: standard catheter lock and taurolidine/citrate catheter lock.

present in the pre-taurolidine/citrate group, but this confounder was corrected in the statistical analysis.

INFECTION RATES

In the pre-taurolidine/citrate group, 14 dialysis catheter infections occurred with a catheter infection rate of 5.2 bacteraemias per 1000 catheter days. In the taurolidine/citrate group, one infection was recorded with a rate of 0.6 per 1000 days. The incidence of catheter infections throughout the study period is shown in Figure 1.

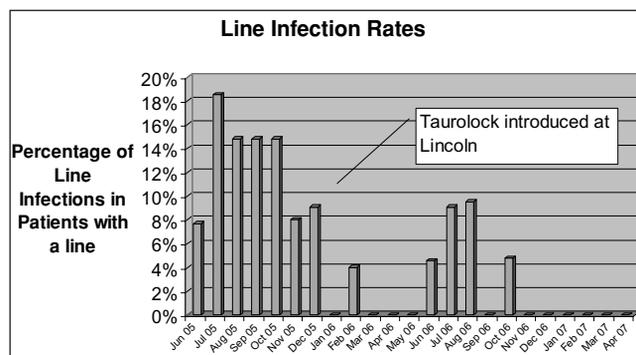


Figure 1: Incidence of Line Infections by Month.

In total, 49.3 days per 1000 catheter days were spent on the catheter sepsis treatment protocol prior to use of the taurolidine/citrate preparation. This dropped to 6.0 days per 1000 catheter days after its introduction. This reduction is highly significant ($p < 0.001$). The relative risk of catheter infection pre/post-introduction of the citrate/taurolidine preparation was 7.84.

The uncorrected odds ratio after the introduction of the new agent versus the preintroduction was 0.09 (95% confidence interval [CI] 0.05–0.18, likelihood ratio test, $p < 0.001$).

Patients with femoral dialysis catheters were significantly more likely to spend time on the sepsis treatment protocol compared to patients with jugular catheters (odds ratio 2.68, 95% CI 1.60–4.50, likelihood ratio test, $p < 0.01$).

A previous infection of the line was a significant confounder (odds ratio 2.70, 95% CI 1.78–4.00, likelihood ratio test, $p < 0.001$) and was included in the model. The patient's gender, age or high immunosuppressive risk were not found to have a significant confounding effect. On correction for a priori confounders (age, catheter site and diabetes mellitus status), a strong main effect remained (odds ratio 0.09, 95% CI 0.04–0.17, likelihood ratio test, $p < 0.01$).

Upon further addition of the significant confounder (prior infection of the catheter) to the model, the strong main effect was still present (odds ratio 0.11, 95% CI 0.06–0.21, likelihood ratio test, $p < 0.001$).

PATTERN OF INFECTION

There was no change in the pattern of organisms causing bacteraemias during the study and no evidence of a change in the bacterial antibiotic sensitivities (data not shown).

FLOW PROBLEMS

In the first month, after changing to the taurolidine/citrate preparation, increased flow problems were noted. An inspection of the haemodialysis catheters revealed plaque formation within the lumens. This problem resolved after the commercial agent was mixed with a small amount of preservative-free heparin. No problems were noted with the stability of the mixture.

COST DATA

The detailed cost data are shown in Table 2. The total costs for the 1802 catheter days prior to use of the citrate/taurolidine mixture were €46,300 (£36,600), and €17,500 (£14,000) for the 1669 catheter days using the mixture, a reduction of €10 (£8.00) per catheter day even after the cost of the taurolidine/citrate preparation was included.

DISCUSSION

Catheter-related sepsis is a major cause of morbidity and mortality in the haemodialysis population (Pisoni et al. 2002; Allon 2003). Previous strategies to address this have included the use of various 'catheter-locking' agents. Primarily, these have focussed on the use of antibiotics, including gentamicin and

Month	Cost of in-patient stays (€)	Cost of line insertion/removal + X-rays (€)	Antibiotic cost (€)	Urokinase cost (€)	Total monthly cost (€)
July 2005	6623.2	249.8	120.1	158.5	7151.6
August 2005	5918.2	249.8	92.7	1444.7	7705.4
September 2005	21044.5	499.6	121.9	1434.4	23100.4
October 2005	2302		41.7	1002.3	3346.0
November 2005	3381.8	249.8	51.2	1311.8	4994.6
Total cost 20 July 2005–30 November 2005			427.6	4051.7	46298.0
Introduction of taurolidine/citrate					
December 2005	2254.8		89.6	1012.6	3357.0
January 2006	No line infections			2050.7	2050.7
February 2006	8549.7	435.5	487.4	547.2	10019.8
March 2006	No line infections			519.1	519.1
April 2006	No line infections			652.0	652.0
May 2006	No line infections			958.80	958.80
Total cost December 2005–May 2006			577.0	5740.4	17557.4

Table 2: Breakdown of costs of line infections by month.

cefazolin (Haimi-Cohen *et al.* 2001; Krishnasami *et al.* 2002; Kim *et al.* 2006). Stability of some of the antibiotic mixtures is sometimes questionable (Anthony & Rubin 1999). To our knowledge, this study is the first independent study to investigate the effect of a commercial taurolidine/citrate preparation on haemodialysis catheter sepsis rates.

The study shows a highly significant reduction in the time spent on line sepsis treatment following the introduction of the taurolidine/citrate preparation as a 'catheter-lock' in our unit. There is a substantial reduction in the associated costs despite the outlay on the taurolidine/citrate preparation.

No changes in the patterns of infection or antimicrobial sensitivity were reported by microbiology during this study. Whilst there is a risk of inducing bacterial resistance to the antibiotics used in low doses on a regular basis, the taurolidine/citrate product is an antimicrobial and anticoagulant agent, but has not been shown in the premarketing studies to stimulate bacterial resistance. No adverse effects were reported in terms of patient's safety events, and this is in keeping with the previous data from the United States, the Netherlands and Israel (Allon 2003; Betjes & van Agteren 2004). In the event that the 'lock' cannot be aspirated at the beginning of a haemodialysis session, an injection of the taurolidine/citrate preparation into the patient results in a rapid

metabolism of the taurolidine to the amino acid taurine, which is naturally occurring and not harmful to the patient. The small volume of 4% citrate solution in the product has not been shown to result in clotting problems or hypersensitivity reactions if injected into the patient. (Taurolock®, Kimal Ag 2005)

There were problems with the catheter flows initially, and this was resolved by mixing the taurolidine/citrate preparation with heparin, as described. A previous study has noted that the catheter patency improved when heparin was added to the taurolidine/citrate solution (Allon 2003). Prior to the introduction of the taurolidine/citrate line lock, the use of urokinase was substantially higher than in the next 6 months of the study, indicating that the taurolidine/citrate mixture improved the catheter patency overall.

This study was not a randomised controlled trial, and a pragmatic resource allocation approach has been adopted in defining the line sepsis rates, rather than a strict microbiological criteria, as this was felt to address our hypothesis with minimal disruption to the ongoing patient care. Because of the design of the study, it uses a noncontemporaneous control group. This limitation has been minimised by consideration of the potential confounders and risk factors for infection (Jean *et al.* 2002; Pawar *et al.* 2004) and consistency of unit procedures (other than the

introduction of taurolidine/citrate) over the studied period. The change in seasons, however, remains an unavoidable potential factor, and further work is indicated to exclude its influence on the observed effect of taurolidine/citrate. However, the reduction in the line sepsis rates continued into the summer months of 2006 at our unit, with a continued use of the taurolidine/citrate line-locking solution. There have been anecdotal reports of increased line sepsis rates over the summer months in some units. There appears to be little in the published literature to support this, although one paper has reported an increase in the central venous catheter infections due to *Acinetobacter* over the months of July to October compared to the period of November to June (McDonald et al. 1999).

CONCLUSION

This study demonstrates that the use of a taurolidine/citrate catheter-locking agent can significantly reduce the number of days for which the haemodialysis patients receive treatment for line sepsis. The costs associated with catheter sepsis treatment were substantially reduced, demonstrating that this was a cost-effective intervention. Since the end of this study, the benefits have been maintained, and the use of taurolidine/citrate has been extended to the rest of the East Midlands Renal Network. The expected confounders for the study were corrected for in the analysis, but the numbers in the study were small, and this was not a randomised controlled trial. Further work needs to be done to confirm the findings.

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