



1. MBBS. Division of Nephrology, Department of Nephrology, Fatima Memorial Hospital, University of Health Sciences, Lahore, Pakistan.
2. MD. Division of Nephrology, Department of Medicine, University of Health Sciences, Fatima Memorial Hospital, University of Health Sciences, Lahore, Pakistan.
3. MD. Division of Nephrology, Department of Medicine, Hashmat Medical and Dental College, Gujrat, Pakistan.
4. MBBS. Division of Nephrology, Department of Medicine, Fatima Memorial Hospital, University of Health Sciences, Lahore, Pakistan
5. MBBS., Division of Nephrology, Department of Medicine,, Fatima Memorial Hospital, University of Health Sciences, Lahore, Pakistan.
6. MBBS, PhD. Department of Community Health Sciences, Fatima Memorial Hospital, University of Health Sciences, Lahore, Pakistan.

Correspondence Address:
Nauman Tarif MD.
Fatima Memorial Hospital,
Lahore, Pakistan.
ntarif@yahoo.com.

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TEMPORARY HEMODIALYSIS; TAUROLIDINE LOCK TO PREVENT CATHETER-RELATED BLOOD STREAM INFECTIONS

Dr. Omer Sabir¹, Nauman Tarif², Sheikh Rizwan³, Kashif Rafique⁴, Nabiha Rizvi⁵, Amanullah Khan⁶

ABSTRACT... Catheter related blood stream infections (CRBSI) in patients undergoing hemodialysis frequently results in significant morbidity and mortality. Attempts at prevention of CRBSI by catheter lock antibiotics, antibiotic combinations or solutions including Taurolidine have emerged over years. **Objectives:** To determine the role of taurolidine lock in presentation of Catheter related infection in hemodialysis. **Design:** Multicentre un-built, randomized controlled, non-inferiority trial. **Period:** Jul 2012 to Dec 2013. **Setting:** Department of Nephrology, Fatima Memorial Hospital UHS Lahore. **Methods:** It was a multicentre, un-blinded, randomized controlled, non-inferiority trial. **Results:** Out of 95 patients, total of 38 patients were randomized into two groups. In group A catheters were locked with Taurolidine 2% and Heparin (5000IU/ml) equal to the catheter volume according to the protocol. In group B (control) catheters were locked with Heparin alone. 36 patients completed the study protocol. For primary end point analysis (30 days) the mean duration of catheter days was 27.25 + 5.5 days (median 30 days). During this period of follow up only one patient from Group B had CRBSI resulting in a point incidence of CRBSI of 2.7%. **Conclusions:** Catheter lock with Taurolidine 2% in combination with heparin compared to heparin alone had no additional benefit in prevention of CRBSI. This however needs to be evaluated in a larger study using non cuffed temporary vascular access (TVA).

Key words: Haemodialysis, Catheter Lock, Catheter Related Blood Stream Infections, Taurolidine.

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INTRODUCTION

Emergency hemodialysis through temporary vascular access (TVA) is a lifesaving intervention undertaken in patients with Chronic Kidney Disease (CKD) stage V without permanent vascular access. Several international associations including European Best practice Guidelines (EBPG) and Kidney Disease Outcomes Quality Initiative (KDOQI) recommend keeping temporary vascular catheter for as short time as possible to prevent catheter-related blood-stream infections (CRBSI) and its complications^{1,2}. In fact, CRBSI amounts to almost one third of the cost of ESRD management with reported mortality rates of 12–25.9%³.

Unfortunately majority of our patients initiate dialysis via temporary vascular access^{4,5,6}. Local experience of three studies describe the rate of CRBSI that are much higher^{4,5,6} than the internationally reported rate of less than 8%⁷. Permanent cuffed catheters result in lesser incidence of CRBSI⁷ however are infrequently used⁶ in our patients due to unavailability and cost issues. Creation of arterio-venous fistula (AVF) and its successful cannulation may take another 4-6 weeks resulting in higher number of catheter days against the current recommendations^{4,5,6,8}.

With these issues in our patients, temporary vascular access is usually needed for initiation of dialysis while waiting for the maturation of AVF. We

therefore carried out the current study in incident CKD V patients presenting for hemodialysis for the first time without an already created or functioning permanent vascular access. We compared the efficacy of Taurolidine catheter lock solution in prevention of CRBSI in such patients when temporary non-cuffed, non-tunnelled double lumen haemodialysis catheter was expected to be kept for duration of 30 days.

MATERIALS AND METHODS

This was a multicentre un-blinded, randomized controlled, non-inferiority trial carried out in two tertiary care hospitals. The study was approved by the Institutional Review Board.

Subjects: CKD stage V patients presenting for dialysis without permanent vascular access.

Inclusion criteria: CKD-V patients requiring haemodialysis, age more than 18 years without permanent vascular access (arterio-venous fistula (AVF), arterio-venous graft (AVG) or cuffed hemodialysis catheters) or with recently created AVF or AVG but without possibility of cannulation for 30 days.

Exclusion criteria: Sepsis at presentation, antibiotic use within 7 days prior to the catheter insertion, pregnancy.

Hemodialysis was performed using Fresenius 4008H machines and bicarbonate dialysate. As per our normal routine, 4 short hemodialysis sessions in the first week (to avoid dialysis disequilibrium syndrome) were followed by twice per week hemodialysis sessions of 4 hours each.

After obtaining informed consent, patients were randomized according to random numbers table into two groups.

Group A: 2% Taurolidine (TauroSept® Geistlich Pharma, Switzerland provided free of cost by Daught & Hak, Pakistan) 1.5 ml mixed with Heparin 1.5 ml (7500 units), was administered into the catheter lumen equal to the recommended volume mentioned on the catheter, at the time of

insertion of catheter and then at the end of dialysis sessions number 1, 2, 4, 6, 8, 10 (Total 4 weeks: four short dialysis in the first week and then twice per week), and with only diluted heparin lock (heparin 1.5 ml diluted in 1.5 ml of normal saline) for rest of the dialysis sessions (3,5,7,9). This was done to assess the intermittent use of Taurolidine due to cost constraints.

Group B: Catheter lumens were filled with 1.5 ml unfractionated Heparin 5000 units per ml mixed with 1.5 ml normal saline, equal to the catheter lumen volume at the end of each dialysis session.

The primary endpoint was completion of 30 days without episode of CRBSI with the same catheter or CRBSI at any point during the study. Patients were also included in final analysis if they came off dialysis after at least 4 sessions of dialysis (i.e.1 week).

Catheters were inserted using real time ultrasonographic guidance. All patients received an antimicrobial cream (mupirocin) to prevent exit site infection and porous sterile dressing was done after each session.

Patients were followed up regularly by the primary investigators until the catheter was removed. At each visit record was made of the catheter insertion site and symptoms suggestive of CRBSI. We defined CRBSI as presence of fever (temperature more than 38°C) during hemodialysis with presence of chills, rigors and/or unexplained hypotension⁹. In the event of suspected CRBSI, two sets of cultures from catheter (one each from arterial and venous port) were sent for confirmation of microbiological diagnosis in accordance with EBPG guidelines¹⁰. Further management of these patients with antibiotics and/or catheter removal was according to standard recommendations.

Means and standard deviation were calculated for age and duration of catheter days whereas percentages were calculated for gender and incidence of CRBSI. Number of catheter days was calculated by summing up individual duration of catheter remaining in situ in each group; sum of

both groups was total number of catheter days in the study cohort¹¹. We also carried out univariate and multivariate analysis to observe the impact of various factors on CRBSI.

RESULTS

Total of 95 temporary catheters were inserted during the study period. Only 38 new patients were finally randomized into the study. 57 patients were excluded as they declined, had femoral catheters, or presented for reinsertion due to malfunctioning catheter or suspected CRBSI. One patient from the heparin group and one patient from taurolidine group were lost to follow up in the first week after randomization and therefore were excluded from the analysis. For final analysis 36 patients were therefore included. The demographic characteristics are given in table I. For primary end point analysis (at 30 days) the mean duration of catheter days was 27.25 ± 5.5 days (median 30 days). 28 patients (Group A= 15, Group B= 13) were able to reach primary end point. 18 patients had their catheter removed on the 30th day, the reasons were: maturation of AV fistula (n=11), change of catheter (n=2), recovery of renal function (n=2), CRBSI (n=1), initiation of Continuous Ambulatory Peritoneal Dialysis (CAPD) (n=1) and sudden cardiac death (n=1). 10 patients reached the primary end point between 7-29 days. Among these four patients had sudden cardiac death, three recovered renal function sufficient to be off dialysis and three other patients (22nd, 26th and 27th days) were switched to AVF. During this period, in Group A no episode of CRBSI was documented, however in Group B one patient had CRBSI on the 28th day of study (patient refused further workup and was treated empirically). This single episode results in a point incidence of CRBSI of 2.7% (1.1/1000 catheter days).

In all, total number of catheter days studied was 741 days (Group A: 380 days, Group B: 361 days).

Univariate and multivariate analysis did not show significant effect of gender, age, number of catheter days or diabetes on CRBSI incidence.

Total number of patients.	36
Group A	17
Group B	19
Mean Age	48.83+13.28 years
Group A	52.87± 12.93 years
Group B	44.29 ±12.51 years
Gender (M:F)	1:1.1
Diabetes	25 (69.4%)
Hypertension	24 (66.9%)
Chronic Glomerulonephritis	9 (25%)
Unknown	2 (5%)

Table-I. Baseline characteristics of all patients.

DISCUSSION

It is evident from this study that unfortunately, still large number of patients initiate haemodialysis in our setting using temporary vascular access and may keep the catheter for more than 4 weeks (median 30 days, in our study). Local experience of three studies describe the rate of CRBSI upto 11.9% to 30% which is quite high^{4,5,6}.

In their study of 50 patients, Sheikh et al place the incidence at around 30%, with femoral catheters being most likely to develop infection (76.9%)⁴. We therefore deliberately did not include femoral catheters in our study due to high infection rates. Anees et al in their retrospective analysis place the infection risk at around 11.9% out of 227 catheter insertions in 177 patients⁵. Of these 227 catheters only 84 (34%) were internal jugular catheters, and the mean duration of catheter stay was 37.14 days. They however did not mention the CRBSI rates in these patients separately according to catheter site. Whereas Qureshi et al reported the incidence of 25% which was similar to Sheikh et al, probably, again due to a high percentage (40%) femoral catheters in these patients also⁶. These incident rates of CRBSI are higher than the internationally reported rate of 8%.⁷ It is therefore more important in our setting due to cost constraints and significant morbidity and mortality, that we undertake measures for prevention of CRBSI.

Since the recent evidence in favour of antimicrobial catheter lock solution is robust, it is therefore gaining widespread use despite concerns about

spill over toxicity and development of resistance against the commonly used antibiotics as catheter locks¹²⁻²⁰.

In our study we used Taurolidine 2% as antibiotic catheter lock solution mixed with equal amount of unfractionated heparin. Previously, Taurolidine was used either with or without citrate and heparin anticoagulant²¹, resulting in obvious benefits in prevention of CRBSI^{16,22-25}.

In our study only one patient (2.77%) from the heparin group had suspected CRBSI. This is statistically insignificant and far better than the local experience. This could be the result of study bias since the technicians and patients may have been more careful in handling these catheters at each haemodialysis session, nevertheless it was a multicentre study with 25% of the patients (n=10) from the second centre.

It will be important to point out that although standard of care suggests keeping un-cuffed catheters for as short time as possible (K/DOQI guidelines)², our patients cannot afford to bear the burden of high cost of permanent cuffed catheters or even reinsertion of non-cuffed catheters every 7 – 10 days till the maturation of permanent vascular access. Even in countries with early referrals and better care of CKD patients, availability of a fistula or a graft at the initiation of haemodialysis is relatively uncommon (AVF: 16.6%, AVG: 4.9%),²⁶ this percentage is arguably higher in our population, although no data exists in literature as yet. Our study does suggest that keeping the temporary un-cuffed catheters for around 4 weeks is possible according to our local needs if proper care is taken, nevertheless we do not encourage delaying AVF creation till CKD–V. The battle of getting CKD patients to understand the need of dialysis and its preparation to avoid significant morbidity and mortality is a never ending struggle in our current circumstances.

We were unable to document any additional benefit of Taurolidine, nevertheless, studies have shown its efficacy in prevention of CRBSI for cuffed haemodialysis catheters²¹ and CVP lines

used for total parenteral nutrition^{22,25,28,29}. CVP lines and permanent catheters have a high risk of infection since these are being manipulated for nutrition and medications on a daily basis, and multiple times during the day. In dialysis patients it is usually the same technician handling the catheter and the frequency is twice per week in our setup. This intermittent use of HD catheter will lead to comparatively less CRBSI incidence as compared to CVP lines.

Being the only randomized controlled trial from our region this study provides insight about the local experience of TVA over 4 weeks. Possibility also exists that overall incidence of CRBSI has declined due to the increasing awareness over time among the dialysis centres and the patients, for the care of TVA each time it is used. This study however, should not be taken as an excuse to delay the creation of AVF and, until we reach the internationally prevalent Fistula first percentage, careful monitoring and infection control practices could allow keeping TVA for a longer period of time.

CONCLUSIONS

Catheter lock with Taurolidine 2% in combination with heparin compared to heparin alone had no added benefit in prevention of CRBSI. This however needs to be evaluated in a larger study using non cuffed temporary vascular access.

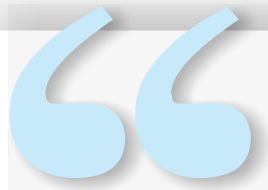
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“A negative mind will never give you a positive life.”

Unknown



PREVIOUS RELATED STUDY

Ahmad Nawaz Bhatti, Saif ud Din Awan, Asiya Anwar. Hemodialysis (Original) Professional Med J Jul-Aug 2012;19(4): 573-580.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Omer Sabir		
2	Nauman Tarif		
3	Sheikh Rizwan		
4	Kashif Rafique		
5	Nabiha Rizvi		
6	Amanullah Khan		