

The Efficacy of Taurolidine Citrate Solution versus Heparin Lock Solution Instilled in the Catheter Lumens of End Stage Renal Disease Patients on Hemodialysis

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ABSTRACT

Background: Hemodialysis patients with end-stage renal illness use a tunnelled central vein catheter for vascular access. Heparin with a preservative, in contrast, exhibits inferior antibacterial effects against biofilm and planktonic bacteria.

Aim: To evaluate the effectiveness of taurolidine citrate solution versus heparin lock solution when infused into the catheter lumens of hemodialysis patients with end-stage renal illness.

Study design: Randomized clinical trial

Place and duration of study: Hemodialysis Unit, King Fahad Specialist Hospital, Buraidah, Saudi Arabia from 11th December 2018 to 10th June 2019.

Methodology: One hundred and fourteen patients on hemodialysis aged 40-70 years with end stage renal disease with Glomerular filtration rate (GFR) less than 15 mL/min, on maintenance hemodialysis through tunnelled dialysis catheter dependent for at least 6 months and patent catheters were selected and randomized into two equal groups by using sealed opaque envelopes bearing a tag of Heparin group and citrate-taurolidine group. Patients were excluded from the study if they had a catheter site infection or an infection unrelated to a catheter that was on antibiotic therapy or had positive blood cultures within two weeks of enrollment. Every two weeks and at the time the catheter was removed, blood cultures were routinely obtained from the catheter lumen to look for bacterial colonization. At the conclusion of six months of hemodialysis, the CRI was assessed. All instances of infections caused by catheters were documented.

Results: Incidence of catheter related infection occurred in 5 (8.8%) patients who underwent Heparin group while none of the patient (0%) of taurolidine/citrate group suffered with catheter related infection. This data reveals significantly high incidence of CRI in Heparin group ($p=0.029$) and significantly high efficacy of taurolidine/citrate group over Heparin group.

Conclusion: Efficacy of taurolidine citrate solution is superior versus heparin lock solution instilled in the catheter lumens of patients on hemodialysis.

Keywords: Catheter, Infection, Renal disease, Hemodialysis

INTRODUCTION

In the United States, 20% of end-stage renal disease patients receiving hemodialysis use a tunnelled central vein catheter to get the vascular access¹. This may be because they are waiting for an arteriovenous fistula (AVF) or arteriovenous graft (AVG) to develop or to be completed, or because their vessels are too small or exhausted to accommodate an AVF or AVG. Infection² and thrombosis are the two main risks associated with tunnelled central venous catheters, particularly if they are retained for an extended period of time. These catheters produce a bacterial biofilm on their inner surface, which leads to infections. Catheter related bacteremia often arise from this bacterial biofilm³. Systemic antibiotics typically have no effect on this biofilm. For this reason, when a dialysis patient contracts a catheter-related infection, he also receives systemic antibiotics and a new catheter. The incidence of catheter-related infections in patients undergoing dialysis can be decreased if bacterial biofilm growth in the catheter's lumen can be avoided⁴. To do this, a concentrated antibiotic solution can be administered into the catheter lumen. Antibiotic catheter locks have been found to decrease the rate of infection and the development or removal of bacterial biofilm in numerous *in vitro* and *in vivo* studies^{4,5}.

According to one study, individuals with hemodialysis who used gentamicin lock solutions experienced much lower catheter-related bacteraemia than those who used non-tunnelled

catheters⁶. Another study found that using gentamicin 320ug/mL in 4% sodium citrate as a catheter lock regularly in central vein catheters in patients receiving maintenance hemodialysis therapy significantly reduced the incidence of catheter-related blood stream infection and the author also reported that it was equally effective as heparin 1,000 U/mL in preventing catheter clotting.⁷

Compared to citrate 46% and heparin, catheter lock solution (CLS) with heparin/gentamicin tends to reduce catheter-related infections (CRI), and, quite bluntly, improves the CRP (C-reactive protein) course following catheter placement.⁸ Taurolidine and citrate is an additional method for catheter locks. A benign, broad-spectrum antibacterial agent with no known resistance is taurolidine. The methylol groups in taurolidine bond permanently to the cell walls of bacteria and fungus, which causes taurolidine to have an antibacterial effect⁹. In one study, out of 39 patients in heparin group, 4 (10.25%) developed catheter related infection as more than two positive blood cultures in twelve episodes for 6 months as compared to taurolidine and citrate group where none of the patients developed CRI in patients on haemodialysis¹⁰.

Annually, 30% of patients with central venous catheters encounter a septic or bacteremic episode, putting them at risk for the long-term morbidity and mortality that come with it¹¹. It causes hospital stays to last longer and costs more money. When a patient doesn't react to antibiotic therapy, it depletes resources for nursing care, antimicrobials, and surgical removal of the catheter. The findings of this study might aid in lowering the cost of these patients' healthcare.

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MATERIALS AND METHODS

From December 11 to June 10, 2018, after permission from Ethical Review Committee 114 hemodialysis patients, 57 each in the heparin and citrate-taurolidine groups were separated into two equal groups for the purposes of this randomized clinical trial at the King Fahad Specialist Hospital in Buraidah, Saudi Arabia. All patients between the ages of 40 and 70 who had end-stage renal disease (GFR15 mL/min), maintenance hemodialysis with a tunneled dialysis catheter, were dependent on a catheter for at least six months, and had patent catheters were included. Patients with positive blood cultures or those who started antibiotic medication before two weeks after enrolment, as well as those who had catheter exit site infections and other foci of infection, were eliminated. Contrary to the taurolidine/citrate group, whose catheters were traditionally locked by a heparin solution at the ending of each dialysis session, the patients in the heparin group had their catheters relocked with the same catheter lock solution at the end of each session under aseptic conditions. Blood cultures were routinely taken from the catheter lumen to check for bacterial colonization every two weeks and after the catheter was withdrawn. The presence of a fever of 380C with rigors and chills during hemodialysis, at least two positive blood cultures, and the absence of any other signs of infection were considered to be signs of catheter-related infection. The CRI was calculated at the end of six months of hemodialysis. All instances of infections caused by catheters were documented. SPSS-25 was used to enter and analyze the data..

RESULTS

There were 60 male and 54 female patients with male to female ratio (1.1:1). The mean age of the patients was 56.31±6.82. Catheter related infection occurred in total 5 patients. Overall incidence of catheter related infection was 5(4.4%). In heparin group, 27(47.4%) were males and 30(52.6%) females while in taurolidine/citrate solution group, 33(57.9%) were males and 24(42.1%) were females. The treated groups either with heparin or with taurolidine/citrate were thus statistically insignificant according to gender (p=0.260) [Fig. 1].

The commonest age group in the both study groups was 51-60 years in which 30 patients of heparin group and 29 patients of taurolidine/citrate solution group were seen followed by age group of 61-70years in which 16(28.1%) patient of Heparin group and 19(33.3%) patients of taurolidine/citrate solution group were seen. Eleven (19.3%) patient of heparin and 9(15.8%) patients of taurolidine/citrate group were found in the age group of 40-50 years and it reveals that both treatment groups were statistically insignificant (p=0.789) according to age (Fig. 2).

Incidence of catheter related infection occurred in 5(8.8%) patients who underwent heparin group while none of the patient (0%) of taurolidine/citrate group suffered with catheter related infection and this data reveals significantly high incidence of CRI in heparin group (p=0.029) [Fig. 3].

Since 100% patients of taurolidine/citrate group were found negative for CRI, it shows significantly high efficacy of taurolidine/citrate group over heparin group (p=0.029) [Fig. 4].

Out of 60 male patients, CRI occurred in 3(5%) patients while in 54female patients, CRI occurred in 2(3.7%) patients. Data reveals statistically insignificant difference of proportion of occurrence of CRI between the genders (p=0.736) [Table 1].

Table 1: Comparison of catheter related infection between the genders

Catheter related infection	Gender		P value
	Male	Female	
Positive	3 (5%)	2 (3.7%)	0.736
Negative	57 (95%)	52 (96.3%)	
Total	60	54	114

Out of 20 patients of age group 40-50 years, CRI occurred in 1(5%) patient while out of 59 patients of age group 51-60 years, CRI occurred in 2(3.4%) patients and out of 35 patients of age

group 61-70 years, CRI occurred in 2(5.7%) patients. This showed statistically insignificant difference of proportion of CRI among the various age groups (p=0.859) [Table 2].

Table 2: Comparison of catheter related infection between the age groups

Catheter related infection	Age (years)			P value
	40-50	51-60	61-70	
Positive	1 (5%)	2 (3.4%)	2 (5.7%)	0.859
Negative	19 (95%)	57 (96.6%)	33(94.3%)	
Total	20	59	35	114

Fig. 1: Comparison of gender between heparin and taurolidine/citrate groups

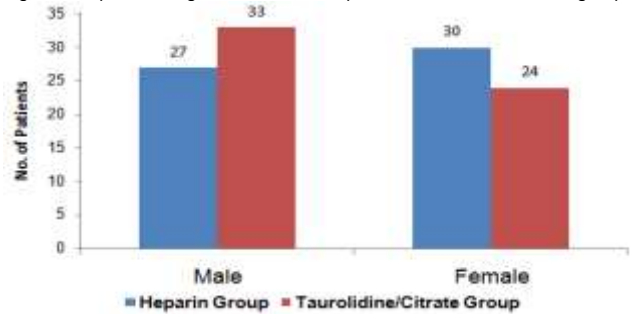


Fig. 2: Comparison of age groups between heparin and taurolidine/citrate groups

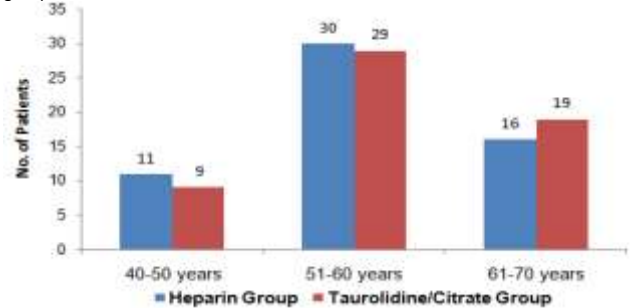


Fig. 3: Comparison of catheter related infection between heparin and taurolidine/citrate groups

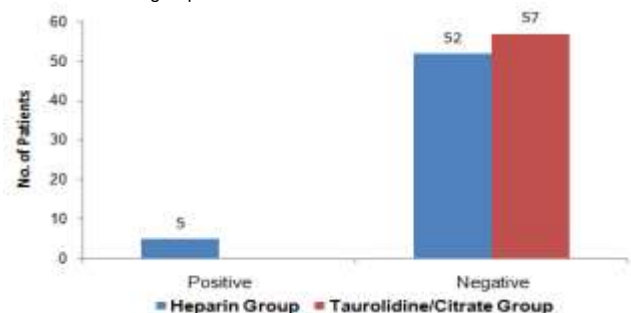
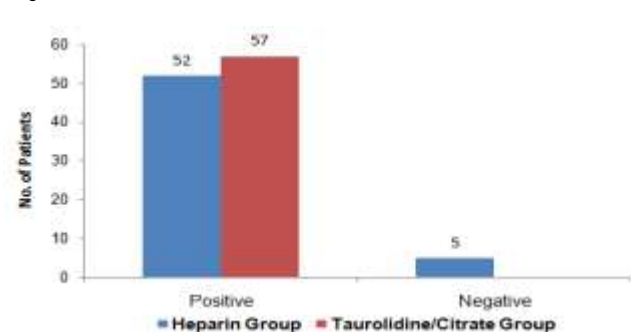


Fig. 4: Comparison of the effectiveness of taurolidine citrate solution with heparin lock solution when administered to hemodialysis patients with end-stage renal illness



DISCUSSION

The results demonstrated that the taurolidine citrate solution prevents 100% the CRI while efficacy of Heparin was 91.2%. Our results are consistent with the reported study in the literature¹⁰. This is a good, expected outcome, as it indicates that if locked in the catheter from the point of catheter insertion into the patient, could potentially prevent CRI in the catheter lumen. Both Gram-positive and Gram-negative organisms tested did not grow biofilm in the presence of the lock solution. Additionally, the supplementary test performed on the biofilm pegs growing in the lock solution after 72 hours confirmed that the organisms were killed, not merely inhibited, by the lock solution.

During the dialysis process, the catheter surface is continuously exposed to blood components like platelets, fibrin, and proteins inside the blood vessel. By allowing microorganisms to adhere to the catheter surface and produce exopolysaccharide, which may then combine with other blood components and further suffocate the biofilm cells, fibrin may promote the growth of biofilm in the catheter lumen.

According to a recent meta-analysis by Jeffer et al., different catheter-locking solutions were used to prevent CRB in seven randomised clinical studies. These antibacterial and antibiotic lock solutions reduced the frequency of CRB, according to the study's findings, without having any detrimental side effects. When an antibiotic lock was utilized, CRB actually occurred 7.72 times less frequently.¹²

In a nonrandomized trial, both removing the old catheter and inserting a new one had an equivalent impact on the patient's likelihood of remaining infection-free.¹³ Even if an interventional procedure is necessary and replacing catheters has a little (low) risk of infection, this approach is still beneficial. Injecting an antibiotic lock into the lumen of the catheter is a rapid and effective alternate technique for getting rid of the bacteria in the biofilm matrix. While the catheter is still in place, this antibiotic-lock solution can be used to help treat the infection as part of systemic antibiotic therapy for CRB. If it is successful, continuous outpatient dialysis would not require an interventional approach. During the examination of Taylor et al., microbiology did not notice any changes in the patterns of infection or antimicrobial sensitivity.¹⁴

The taurolidine/citrate has not been shown in premarketing studies to increase bacterial resistance, even though there is a risk of doing so when antibiotics are administered regularly in low dosages. Additionally, no adverse events involving patient safety were identified; this is consistent with earlier findings from Israel, the Netherlands, and the United States^{15,16}.

In a recent double-blind control experiment, which was designed to assess the effectiveness of catheter limited filling with cefotaxime and heparin to evade CRI. The results of the experiment showed the probability of tunnelled catheter-related infections (CRI) was considerably lesser in the cefotaxime group when the researcher compared to the control group (p 0.001). No group experienced exit site infections¹⁷.

Despite the fact that we only included ESDR patients who were clinically stable, limited studies on the use of DC antimicrobial locks in critically ill patients showed that citrate locks were 46.7% more effective than saline locks for postponing DC-related infections. However, the citrate (24/1,000 catheter days) and saline (30/1,000 catheter days) groups had the highest rates of DC-related blood stream infections¹⁸.

More research is needed before recommending the use of any antimicrobial locks for treating or preventing DC infections, despite the fact that a number of them appear promising.

CONCLUSION

The outcome of our research is quite promising. The results prove the efficacy of taurolidine citrate solution is superior versus heparin lock solution instilled in the catheter lumens of patients on hemodialysis.

Conflict of interest: Nil

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