ROLE OF ETHANOL LOCK THERAPY VS HEPARIN LOCK IN PREVENTING INFECTIONS IN NON-TUNNELED HEMODIALYSIS CATHETERS

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ABSTRACT

INTRODUCTION: This study aims to determine the rate of catheter related bloodstream infection using intraluminal 70% ethanol lock 20 min prior to initiation of hemodialysis in comparison with heparin lock and also to study adverse events with the use of locks.

MATERIAL AND METHODS: Out of 196 patients, eligible 128 patients who under went hemodialysis in Tribhuwan University Teaching Hospital, were randomly allocated to 68 jugular catheterization with ethanol lock or heparin lock and 60 femoral catheterization with ethanol lock or heparin lock. 5 patients with jugular catheter with ethanol lock and 3 patients with heparin lock changed center. The major outcomes were catheter-related blood stream infection (CRBSI) or thrombosis or other adverse effects.

RESULTS: According to KDIGO definition of CRBSI, definite CRBSI occurred in 22 (18.33%) patients in Heparin group, probable CRBSI occurred in 31 (25.83%) patients in Heparin whereas definite CRBSI occurred in 1 (1.38%) patient in Ethanol group, and possible CRBSI occurred in 18 (15.00%) patients in Ethanol group. Most common organisms isolated were Staphylococcus aureus and Enterococcus faecalis in heparin group. No adverse events occurred in ethanol group.

CONCLUSION: Our study has suggested Ethanol lock therapy is effective in preventing CRBSI as there were fewer CRBSI in ethanol lock in comparision to heparin lock which needs to studied in large population.

KEYWORDS: Ethanol lock therapy, Heparin lock, CRBSI

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INTRODUCTION

Vascular access is the Achilles' heel for patients requiring hemodialysis.[1] Although the techniques for sustainable vascular access have developed since 1960 after first successful cannulation of blood vessels by Scribner et al.[2], majority of the ESRD patients initiate renal replacement therapy in the form of hemodialysis (HD) through the non-tunneled vascular catheter.[3,4] AV fistula is a better vascular access but it needs several weeks to mature and fistula failure[5] prompts use of non-tunneled vascular catheter as a bridge to hemodialysis. This catheter can be a source of infection if it gets colonized with micro-organism from the exit-site of catheter or through the catheter hub. Bacterial migration through the hub or the exit site and growth on the surface of catheter with biofilm formation occurs within a day of catheter placement.[6] Catheter related bacteremia often arises from this biofilm which not only leads to complications but also increased morbidity, length of hospitalization, costs and mortality. Systemic antibiotics are of little help in eradicating microorganisms because of their poor penetration in the biofilm.[7-8] Locking the catheter with a variety of antibiotics[9] and anticoagulants[10] have been tried to eradicate organisms from biofilms, but their use have decreased as they have limited spectrum, lead to resistant strains and there is risk of systemic toxicity.[11,12] Ethanol lock therapy could be an alternative since it is bactericidal and fungicidal and development of resistance is not known.[13,14] Furthermore, ethanol possesses intrinsic anticoagulant activity, as evidenced by the use of ethanol to restore catheter patency.[15] It is cost-effective. So there are studies when catheter salvage has been tried without complications[16] or with ethanol lock therapy.[17] We studied the effect of ethanol lock therapy in preventing catheter related bloodstream infections in non-tunneled temporary vascular catheters among Nepali population, where no previous such studies has been done in our settings.

MATERIAL AND METHODS

Patients requiring hemodialysis at Tribhuvan University Teaching Hospital (TUTH) in whom a non tunneled hemodialysis catheter is inserted in the femoral vein (in bed bound patients) or in the internal jugular vein (in ambulatory patients) with eligible criteria after informed consent were included in the study from July 2014 till August 2015. Patients were followed from the day of catheter insertion to the day the catheter was no longer needed or any adverse events occurred prompting removal of catheter. The exclusion criteria were Active sepsis at the time of catheter insertion, Patients on intravenous /oral antibiotic therapy, Mechanical complications while inserting central venous catheter (CVC) like hematoma/ pneumothorax.

The patients were randomized to one of two arms: **A.** Ethanol (70%) [1.4 ml ethanol to be taken in syringe and then 0.6 ml sterile water for injection to be taken in same syringe] **B.** Heparin 1000 IU/ml with Normal saline.Each solution to be designated as either solution A or solution B and was prepared in treatment room and served in 3ml syringes with numbers and label of A or B to HD nurses. The designated lock solution to be used for the entire study or till the CVC is in place. Patient demographic data was collected including age, gender, presence of diabetes mellitus, etiology of renal disease, hemoglobin, serum ferritin, serum albumin at entry into study. Catheter used was Mahurkar double lumen polyurethane hemodialysis catheter in both groups. Outcomes were: I) CRBSI as defined by Kidney Disease Outcomes Quality Initiative (KDOQI) as Definite / Probable / Possible CRBSI (according to KDOQI- Vascular access guideline 2006) .[18] Moreover, for the definite diagnosis of CRBSI, Infectious Disease Society of America (IDSA)[19] criteria was also included.

Definite bloodstream infection: Isolation of the same organism from a semi-quantitative culture of the catheter tip by roll-plate method (>15 colony-forming units per 5cm catheter segment) and from a peripheral or catheter blood sample in a symptomatic patient with no other apparent source of infection. (KDOQI[18])

Probable **bloodstream infection:** Defervescence of symptoms after antibiotic therapy with or without removal of catheter, in the setting in which blood cultures confirm infection, but catheter tip does not (or catheter tip does, but blood cultures do not) in a symptomatic patient with no other apparent source of infection.

Possible bloodstream **infection:** Defervescence of symptoms after antibiotic treatment or after removal of catheter in the absence of laboratory confirmation of bloodstream infection in a symptomatic patient with no other apparent source of infection.

Bacteremia was treated by the attending nephrologist using appropriate antibiotics. II) Catheter thrombosis as defined for persistent flow <200ml/min after ruling out mechanical causes and the presence of thrombosis was confirmed by dissecting the catheter on removal. National Kidney Foundation (NKF)-KDOQI[18] definition for poor flow in tunneled cuffed catheter is blood flow <300ml/min. However as the maximum blood flow through the non-tunneled HD catheter is 250-300ml/min, poor flow was taken as <200ml/min. All study patients who had poor flow (<200ml/min) were to be evaluated in the following manner-- to rule out all the mechanical factors like kink, patient position. If persistent flow <200ml/min despite correcting for mechanical factors, then catheter to be removed and cut to look for presence of thrombus. Femoral access groups were assessed daily for disproportionate swelling of leg with femoral catheter and once it appeared findings of DVT confirmed by colour doppler of leg vesssels to rule out thrombus. Statistical analysis was done using the independent t-test for mean values, Chi-square test and Fisher Exact test were used for the contingency tables with categorical values. The Kaplan-Meier method was adopted for the survival analysis and the comparision of the survival curve was done by using Log Rank (Mantel-Cox) test. SPSS 17 was used for analysis.

RESUTS

196 patients were assessed for eligibility, of whom 128 underwent randomization; 30 patients were assigned to receive ethanol in jugular catheters and 30 patients assigned to receive ethanol in femoral catheters as 8 patients changed the center and were excluded from final analysis. Therefore 30 patients in each group were analysed. A total of 13 patients in the heparin group and 12 in the ethanol group with femoral catheters completed the study before the occurrence of CRBSI or thrombosis as either continuous ambulatory peritoneal dialysis (CAPD) was done or Acute Kidney Injury (AKI) recovered or discharged with jugular catheters or AV graft functional. A total of 17 patients in heparin group and 22 patients in ethanol group with jugular catheters completed the study before the occurance of CRBSI or thrombosis as either AV fistula matured or AV graft functional or spontaneous expulsion of catheter occurred or AKI recovered or renal transplant was done. The study groups had similar age sex distribution. The common native kidney disease (NKD) was chronic kidney disease stage-5 (CKD-5) secondary to HTN associated Kidney Disease- 20 in heparin and 25 in ethanol and CKD-5 secondary to Diabetic Nephropathy- 14 in heparin and 18 in ethanol. CKD-5 secondary to IgA nephropathy was NKD among 6 heparin and 4 ethanol groups. The study groups had hemoglobin, albumin, calcium, phosphorous, alkaline phosphatase and transferrin saturation similar with no statistical difference (p-value >0.05) but heparin group had higher ferritin level in comparision to ethanol group with was statistically significant (p-value<0.05). Table 1. shows among the 72 patients with CRBSI according to KDIGO, definite CRBSI occurred in 22 (18.33%) patients in Heparin group, probable CRBSI occurred in 31 (25.83%) patients in Heparin whereas definite CRBSI occurred in 1 (1.38%) patient in Ethanol group, and possible CRBSI occurred in 18 (15.00%) patients in Ethanol group.

Table 1 : Incidence of CRBSI according to KDIGO

Current Venous Access	CRBSI KDIGO	Lock solution		Total
		Heparin	Ethanol	
Femoral	Definite	4	0	4
	Probable	8	0	8
	Possible	16	12	28
Jugular	Definite	6	0	6
	Probable	4	1	5
	Possible	15	6	21
Total		53	19	72

Table 2: overall non-elective catheter loss

Overall	Heparin (n = 60)	Ethanol (n = 60)	Chi-square test p-value
CRBSI in both accesses	22 (blood culture positive =10)	1 (culture positive = 1)	
Thrombosis (poor flow) in jugular catheters	2	0	
Thrombosis (DVT) in patients with femoral catheters	4 (blood culture positive =1)	0	
Total	28	1	< 0.001

Table 2 shows incidence of poor flow even after ruling out kink or manipulation occured in left internal jugular vein catheter and one right internal jugular catheter with heparin lock. Four cases of DVT (deep vein thrombosis) in ipsilateral leg with femoral catheter inserted side occurred in heparin locked patients. Total number of catheter lost was more in heparin group which is statistically significant (P<0.001).

Table 3 shows majority of the organisms isolated were Staphylococcus aureus and Enterococcus faecalis in femoral and jugular accesses with heparin lock. Acinetobacter baumannii-calcoaceticus Complex was isolated in femoral catheter with heparin lock and jugular catheter with ethanol and heparin lock. Citrobater fruendii isolated in femoral catheter with heparin lock. klebsiella pneumonae and pseudomonas aeruginosa isolated in jugular catheter with heparin lock. There were more culture positive in heparin group.

Fig. 1 shows in patients with Femoral access, overall comparison of the survival curve of the catheter with respect to the event of CRBSI shows that the curve of the more events in the heparin group and the survival of the ethanol group was longer as compared to the heparin group. This was statistically significant at 95% confidence interval with Log-Rank Test p-value 0.001 which is less than 0.05.

Table 3 : Pathogens responsible for crbsi

Organism*Lock solution Cross tabulation in femoral				
Organism		Lock solution(E=Ethanol/ H=heparin)		Total
		Heparin	Ethanol	
Femoral	Staphylococcus aureus	3	0	3
	Enterococcus faecalis	3	0	3
	Acinetobacter baumannii-calcoaceticus Complex	1	0	1
	Citrobacter fruendii	1	0	1
	Total	8	0	8

Organism * Lock solution Cross tabulation in jugular				
Organism		Lock solution(E=Ethanol/ H=heparin)		Total
		Heparin	Ethanol	
Jugular Access	Staphylococcus aureus	2	0	2
	Enterococcus faecalis	1	0	1
	Acinetobacter baumannii-calcoaceticus Complex	1	1	2
	Klebsiella pneumonia	1	0	1
	Pseudomonas aeruginosa	1	0	1
	Total	6	1	7

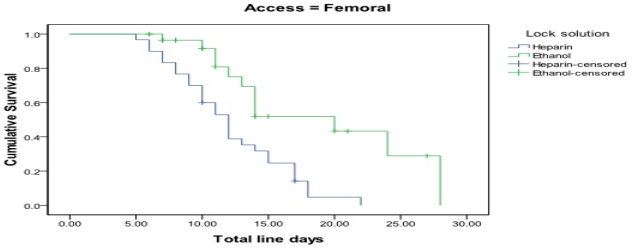

Figure 1 : Survival Analysis of Femoral Access

Fig. 2 shows in patients with Jugular access, overall comparison of the survival curve of the catheter with respect to the event of CRBSI shows that the curve of the more events in the heparin group and the survival of the ethanol group was longer as compared to the heparin group. This was statistically significant at 95% confidence interval with Log-Rank Test p-value 0.000 which is less than 0.05. The Kaplan Meir survival curve shows difference between the two groups for a period of 60 days, however after that the number of patients with catheter decreased hence it is difficult to comment.

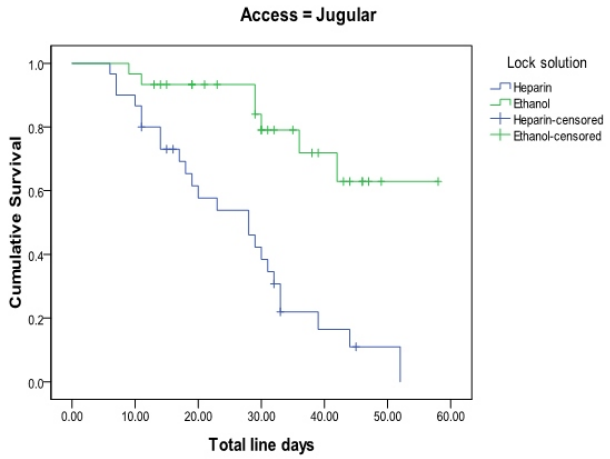

Figure 2 : Survival Analysis of Jugular Access

Venous Access	Lock Solution/ Catheter Days	Number at Risk (Number of CRBSI)					
		10	20	30	40	50	60
Overall	Heparin	60 (12)	48 (26)	17 (6)	11 (6)	3 (1)	1 (1)
	Ethanol	60 (2)	49 (9)	28 (5)	17 (2)	8 (1)	1 (0)
Femoral	Heparin	30 (9)	21 (18)	1 (1)	0 (0)	-	-
	Ethanol	30 (1)	20 (8)	6 (3)	0 (0)	-	-
Jugular	Heparin	30 (3)	27 (8)	16 (5)	11 (6)	3 (1)	1 (1)
	Ethanol	30 (1)	29 (1)	22 (2)	17 (2)	8 (1)	1 (0)

The numbers in parenthesis in the table below x axis are the number of patients in whom an episode of CRBSI occurred in the interval between follow-up assessments.

DISCUSSION

The purpose of this study was to evaluate the impact of concentrated ethanol lock, administered 20 minutes before dialysis initiation, on the rate of CRBSI in non tunneled hemodialysis catheters compared to heparin lock. The main results of the study are that CRBSI occurred with more frequency in heparin group in comparision to ethanol group which is comparable with studies done by Sanders et. Al[20] and it occurred later in ethanol group than in heparin group and also many of them were culture negative. However, catheter thrombosis and bleeding from exit site was higher in heparin group. Thus overall catheter loss was higher in heparin group mainly due to infection than thrombosis and uncontrolled bleeding from exit site.Ethanol has both bactericidal and fungicidal properties and development of resistance is not known.[13] Furthermore, it has been reported that ethanol appears to possess intrinsic anticoagulant activity, as evidenced by the use of ethanol to restore catheter patency[15] and it is cost-effective.

Heparin is the most commonly used interdialytic lock solution because of its anticoagulant properties; however it lacks antibacterial properties hence not effective in prevention of CRBSI. Ethanol lock therapy has been used successfully in treatment of CRBSI in dialysis population.[17,21-23] For the above reasons we tried catheter locking with ethanol for prevention of CRBSI.

The positive finding of this study is that CRBSI occurred with lesser frequency in ethanol groups which echoes with the findings of previous in vivo studies by Mouw et al.[24] ,and Sanders et al.[20] done to evaluate ethanol as a catheter locking solution in non-dialysis setting, where also the incidence of CRBSI decreased. CRBSI occurred later in ethanol group than in heparin group and also many of them were culture negative which coincides with study done by Broom et al.[25]

However, in our study we had two incidence of catheter thrombosis with heparin lock compared to use of ethanol as a lock, the reasons may be due to inadequate heparin locking dosage[26] or leakage[27] or gravitational loss from catheter lumen into systemic circulation.[28] Patency of catheter lumen in ethanol lock might be due to

1) Concentration of ethanol An ethanol concentration above 40% is required to inhibit bacterial growth in established biofilms.54 When instilled into a CVC at a concentration between 40% and 100%, ethanol has been shown to be rapidly bactericidal and fungicidal in vitro, with no concern for development of resistant organisms.[29] A major limitation in the use of high concentrated ethanol for interdialytic locking could be the occurrence of catheter dysfunction that might compromise catheter duration or impair HD performance. A study in which 100% ethanol was used to lock catheter lumens for 24 hours resulted in total occlusion of one out of three catheters.[29] We choose to use a 70% ethanol lock solution because this concentration has been shown to be bactericidal in established biofilms and based on previous reports. [29,30]

2) Duration of catheter lock with ethanol Balestrino et al[13] state that, a significant 3-log reduction in the number of biofilm-associated gram-positive cocci occurred already after 20 minutes exposure to a 60% ethanol lock solution. A dwell time of 30 minutes was required for complete eradication in order to kill established biofilms of gram-positive and gram-negative organisms and candida but Qu Y et al[31] showed that an exposure time of 1 minute to a 70% ethanol solution was sufficient for the sterilization of a bacterial biofilm.

For the above and practical reasons we tried catheter locking with ethanol 20 minutes prior to initiation of every hemodialysis session for prevention of CRBSI. This was

decided because a longer dwell time would have interfered too much with patient care. We feel that an effective strategy would be, along with catheter exit site care, to expose catheter lumens to 70% ethanol for a period of 30 minutes prior to dialysis, which would sterilize the biofilm. The ethanol solution be then withdrawn and followed by a routine dialysis session.

The absence of adverse event in ethanol group might be due to consideration of major limitation in the use of high concentrated ethanol for interdialytic locking, that could have caused catheter dysfunction that might compromise catheter duration or impair HD performance. A study in which 100% ethanol was used to lock catheter lumens for 24 hours resulted in total occlusion of one out of three catheters.[29]There are numerous reports in the literature of repeated exposures to concentrated ethanol between 60 and 70% as a flushing solution and as a lock without impairment of catheter function but the dwell time of ethanol exposure was short and never exceeded 24 hours.[15,20,24,25,31-34]

In our study, the ethanol lock was in place only during 20 min prior to initiation of every hemodialysis session and post dialysis the lumens were locked with heparin during the interdialytic period (48-72 hours) which may have been the reason for none catheter thrombosis in this group.

Similar to other studies performed in non HD adults and infants in whom ethanol was used for preventing or treating catheter-associated infections,[15-17] no adverse reactions were reported our study after the instillation of the ethanol lock.

3) Ethanol solution in isolation with anticoagulant effect Citrate solution mixed with higher concentrations (>30%) leads to precipitation of citrate and ethanol inactivates heparin solution. Hence we did not consider using concentrated ethanol lock in association with heparin or citrate. Also there were few reports that ethanol has some anticoagulant properties[15] which tempted us to use ethanol 70% ethanol in isolation.

Also, heparin locking be done for interdialytic period so that the catheter loss to thrombotic episodes is prevented. However, heparin locking dosage should be adequate[26] in patients without risk of bleeding as there were increased rate of thrombosis in our patients on heparin lock which occurred as in other study[35] with used dose heparin lock which might be due to leakage[27] or gravitational loss.[28] However further studies are necessary to determine the adequate dose of heparin lock to avoid thrombosis along with minimization of bleeding risk. There was one bleeding from exit site of right internal jugular vein catheterized patient with heparin lock which did not stopped after external compression with adrenaline soaked gauze for 1 hour and this type of complication has been reported in other study.[36]

Thus as such 70% ethanol may not cause thrombosis when kept for few hours; however prolonged exposure might result in catheter dysfunction. As ethanol lock was kept for 20 mins only in this study, there were no complications as such which correlates with study by Crnich et. al.[32] where 9 weeks exposure to ethanol had no significant effect on mechanical properties of catheter and study by Landry et. al where 26 weeks exposure to ethanol had no effect on ultrastructure of catheter.[37] We feel that an effective strategy would be - along with catheter exit site care, exposure of catheter lumens to ethanol 70% for a period of 30 minutes pre-dialysis would sterilize the biofilm. The ethanol solution be then withdrawn and followed by a routine dialysis sessions.

CONCLUSION

Using ethanol 70% as a catheter locking solution, locked for 20 minutes before initiation of every hemodialysis session, is safe and effective compared to heparin lock in prevention of CRBSI

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