ORIGINAL ARTICLE
Journal of Indonesia Vascular Access (*INAVA)* 2021, Volume 1, Number 1: 8-15

Published By : IVAA
the Indonesian Vascular Access Association

Comparison of ethanol lock and heparin lock solution as prevention of catheter-related bloodstream infection in hemodialysis patients: systematic review and meta-analysis of randomized controlled trials

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Received: 2021-04-26
Accepted: 2021-06-02
Published: 2021-06-16

ABSTRACT

Introduction: Catheter-related bloodstream infection (CRBSI) is a common complication of catheter use for vascular access in hemodialysis patients and a major cause of morbidity and mortality. Preventive measures, including antibiotic lock, are inadequate due to the risk of resistance and insufficient effect against bacterial biofilm. Ethanol, an antimicrobial substance, is a potential prophylactic lock-in preventing CRBSI. This study aims to assess ethanol lock's effectiveness in preventing CRBSI in hemodialysis patients with a catheter as vascular access and its impact on catheter dysfunction.
Methods: Researchers systematically searched online databases including Pubmed, Cochrane Library, and Science Direct for relevant randomized controlled trials (RCTs) published within 2011 until 2020. Relevant data were pooled in PICOs (Population, Intervention, Control, Outcomes) format and analyzed with Review Manager (version 5.3.5, Cochrane Collaboration, Denmark).
Results: Seven RCTs involving 453 patients were assessed. The primary outcome indicates that prophylactic ethanol lock significantly reduces the incidence of CRBSI compared to that of heparin lock (RR=0.32, 95% CI 0.12-0.83, p=0.02, heterogeneity I^2=68%). The secondary outcome suggests no significant difference in the incidence of catheter dysfunction in ethanol lock and heparin lock (RR=0.75, 95% CI 0.23-2.40, p=0.63, heterogeneity I^2=68%).
Conclusion: Ethanol is a potential prophylactic lock agent in preventing CRBSI in hemodialysis patients with catheter access. Further research is needed to synchronize the procedural use of ethanol lock and evaluate its long-term effect.

Keywords: Catheter-related bloodstream infection, CRBSI, ethanol lock, hemodialysis, heparin lock
Cite This Article: Rosalie, A., Putra, M.A. Bachtiar, M.R., Christian, D.H., Joalsen, I. 2021. Comparison of ethanol lock and heparin lock solution as prevention of catheter-related bloodstream infection in hemodialysis patients: systematic review and meta-analysis of randomized controlled trials. *Journal of Indonesia Vascular Access* 1(1): 8-15. DOI : 10.51559/jinava.v1i1.7

INTRODUCTION

Chronic Kidney Disease (CKD) remains a disease with high worldly prevalence. In late 2016, it is estimated that 3,7 million of the world population suffer from end-stage renal disease (ESRD), and this number continues to increase by 6% yearly. Around 3 million of them require hemodialysis (HD).[1] In Indonesia, according to The Indonesian Renal Registry (IRR), the number of CKD patients increased from 9.649 in 2010 to 30.831 in 2017, while the prevalence increased from 11.484 in 2010 to 77.892 in 2017.[2] Hemodialysis, particularly in Indonesia, remains the main treatment modality. There was a three-fold increase in the number of hemodialysis patients in 2011 than that in 2007. In the dialysis unit on Dr. Soetomo District Hospital Surabaya, the recorded number of CKD patients who undergo routine hemodialysis constantly increased for three years: 245 patients in 2013, 255 patients in 2014, and 303 patients in 2015.[3]

Creating vascular access is a common procedure to aid in hemodialysis procedure. Several known types include catheter access, arteriovenous fistula (AVF), an arteriovenous graft (AVG). AVF and AVG, which are typically used for long-term use, require maturation for about six weeks, during which time patients are usually equipped with temporary catheter access for hemodialysis. The primary failure rate of AVF ranges between 30%-70%, and its 1-year patency ranges around 40%-70%.[4,5] The complication of AVF and AVG, such as thrombosis or stenosis, requires repairing, catheter access is utilized to enable uninterrupted hemodialysis cycles. Furthermore, if possible physiologic sites for AVF or AVG are depleted due to recurrent failure, permanent catheter access may be considered.[4]

Around 80% of patients initiate hemodialysis with a central venous catheter (CVC), which is used in continuation up to 90 days (68,5%) and one year in the form of a tunneled catheter (21%).[6,7] The long-term use of catheters carries risks, including catheter-related infection might occur on the exit site, inside the lumen, and bacteremia (catheter-related bloodstream infection/CRBSI). The incidence of vascular catheter-related bacteremia ranges around 48%-73%, responsible for 26% of catheter removal.[6] In 2011, The United States Centers for Disease Control and Prevention (CDC) reported 41000 cases of CRBSI which resulted in increased hospital admission rates.[8] Hemodialysis patients with CVC are at a 15-fold risk of CRBSI, with mortality rates ranging from 12% to 25%. The risk of sepsis with CVC is 8-fold greater than that with AVG and AVF.[7] Other complications include septic arthritis and epidural abscess.[9,10] CRBSI in hemodialysis patients with a long-term catheter is a nosocomial infection problem with high morbidity and mortality, resulting in higher cost and longer hospital stay. The main causative agent of CRBSI is Gram-positive coccus and Gram-negative basil and fungi that form biofilm on the catheter lumen. In non-permanent catheters, its removal may solve the problem, while in a permanent catheter, antimicrobial lock solutions might be of use.[11]

Antimicrobial locks are further grouped into antibiotic-based and non-antibiotics. The current use of catheter locks commonly consists of heparin, which some studies suggest might aid in forming pathogenic biofilm inside the catheter lumen.[6] The use of antibiotics also raises concerns about antibiotic resistance. Several studies reported resistance in the use of high-dose gentamycin (4-27 mg/ml) against *Enterobacteriaceae sp.* and *Staphylococcus sp.* and one case of death in the use of 1-4 mg/ml gentamycin lock.[6,7] Therefore, current use suggests low-dose antibiotics or replacement of heparin with other agents. However, low-dose antibiotics do not solve the concern for antibiotic resistance.[12] Other studies reported that antibiotics have inadequate biofilm penetration potency. Heparin replacement is deemed irrational due to its greater benefit of thrombus prevention than the risk of biofilm formation.[8]

Due to the concern of antibiotic resistance with its use for locking agents, the authors evaluated the role of non-antibiotic antimicrobial lock solutions. The use of both low- and high-dose trisodium citrate result in inconsistent outcomes related to CRBSI. It is also not recommended due to a case of death and possible induced paresthesia and arrhythmia (by hypocalcemia or systemic embolism). Furthermore, its use requires a higher dose of thrombolytics to reduce catheter dysfunction.[6,7] Ethanol is a widely available, inexpensive antiseptic agent with bactericidal and fungicidal activity. It is a broad-spectrum agent that works through nonspecific protein denaturation and lipid dissolution. Several *in vitro* studies have reported its effectiveness against pathogenic biofilms.[8,11] High-dose ethanol exposure has not been proved to induce resistance with a minimum side effect.[13] This study aims to evaluate the potency of ethanol lock in preventing CRBSI in hemodialysis patients in the form of meta-analysis from available clinical trials.

METHODS

Relevant keywords, consisting of *("Ethanol lock")* AND (*"Heparin lock"*) AND *("Catheter-Related Bloodstream Infection"* OR *"CRBSI"* OR *"Catheter-Related Infection"* OR *"CRI")* AND *("Hemodialysis")* were inputted in search engines, including Pubmed, Cochrane Library, and Science Direct. Data pooling was done during January 2021 to February 2021. Acquired studies were initially screened to exclude non-human studies, non-RCTs, unrelated study topics (unrelated to systemic infection due to catheter as vascular access in regular hemodialysis patients), and studies published languages other than English and Indonesian. Authors identified RCTs regarding the effect of ethanol compared to heparin lock in CRBSI in hemodialysis patients. After eliminating duplicates, 62 studies were found. Further screen resulted in 17 studies that met the inclusion criteria and seven studies with relevant results.[14-19] Data were extracted in a table. Collected studies were then reviewed to ensure synchronous outcomes and enable comparation. This study is in line with the PRISMA flow diagram. The risk of bias was assessed with The Cochrane Collaboration Tools. Quantitative analysis was done to calculate Risk Ratio (RR) and 95% Confidence Interval (CI) with a fixed-effect model (or random-effect model if there is significant heterogeneity/I^2 >50%) using Review Manager software 5.3 (version 5.3.5, Cochrane Collaboration, Denmark). This study aims to evaluate the effect of ethanol lock in the incidence of CRBSI compared to heparin lock in hemodialysis patients as a primary outcome and the effect of ethanol lock in catheter dysfunction as a secondary outcome.

RESULTS

Study Characteristics

The study selection process is shown in Figure 1. All 7 studies that met the inclusion criteria are randomized controlled trials (RCTs). The characteristics of the 7 studies are shown in Table 1. In total, 453 patients are included in this meta-analysis, 228 of whom were treated with ethanol lock and the remaining 225 were control population with heparin lock. All patients were non-pregnant, non-breastfeeding adults (>18 years) who were on regular hemodialysis treatment (urgent/emergency cases and critical ICU patients were excluded). Three studies included participants who undergo hemodialysis due to CKD.[13,18,19] while in three other studies, no etiological diseases were recorded.[14-17] One study included various etiology (CKD secondary to hypertension and diabetes, as well as IgA nephropathy). Four studies used tunneled catheters and 3 studies used non-tunneled catheters.[15,17-19]

All inclusion studies used catheter lock 3x/week (all populations had 2 HD sessions per week). CRBSI in all included studies and as the primary outcome of this study is based on the Kidney Disease Outcomes Quality Initiative (KDOQI) (2006) criteria as definite/probable/possible CRBSI, further defined as:

a) Definite bloodstream infection: Isolation of the same organism from a semiquantitative culture of the catheter tip (>15 CFU/catheter segment) and a blood culture in an asymptomatic patient with no other apparent source of infection.
b) Probable bloodstream infection: Defervescence of symptoms after

antibiotic therapy with or without catheter removal in the setting in which blood culture confirms infection, while catheter tip does not (or catheter tip does, but blood culture does not) in an asymptomatic patient with no other apparent source of infection.

c) Possible bloodstream infection: Defervescence of symptoms after antibiotic therapy or after catheter removal in the absence of laboratory confirmation of bloodstream infection in an asymptomatic patient with no other apparent source of infection.

Catheter dysfunction is a secondary result in this study, in which only 4 included studies evaluated catheter dysfunction. The criteria of catheter dysfunction from each study are further explained in Table 1. In the study by Sofroniadou *et al.* (2017), catheter dysfunction is defined as thrombosis. The inability to use the catheter at >200 ml/minute flow despite additional flushing and instillation of t-plasminogen activator as intraluminal thrombolysis.[19] Shresta & Raut (2015) defined catheter dysfunction as persistent <200 ml/minute flow after eliminating mechanical factors (kink or patient positioning). It evaluated the presence of thrombus by cutting the catheter following its removal.[17] Broom *et al.* (2012) defined catheter dysfunction as flow dysfunction (blockage or reduced flow) and mechanical dysfunction (ruptured catheter).[14] Vercaigne *et al.* (2015) described catheter dysfunction as two consecutive dialysis sessions with a flow of <300 ml/minute for at least 50% dialysis session.[18]

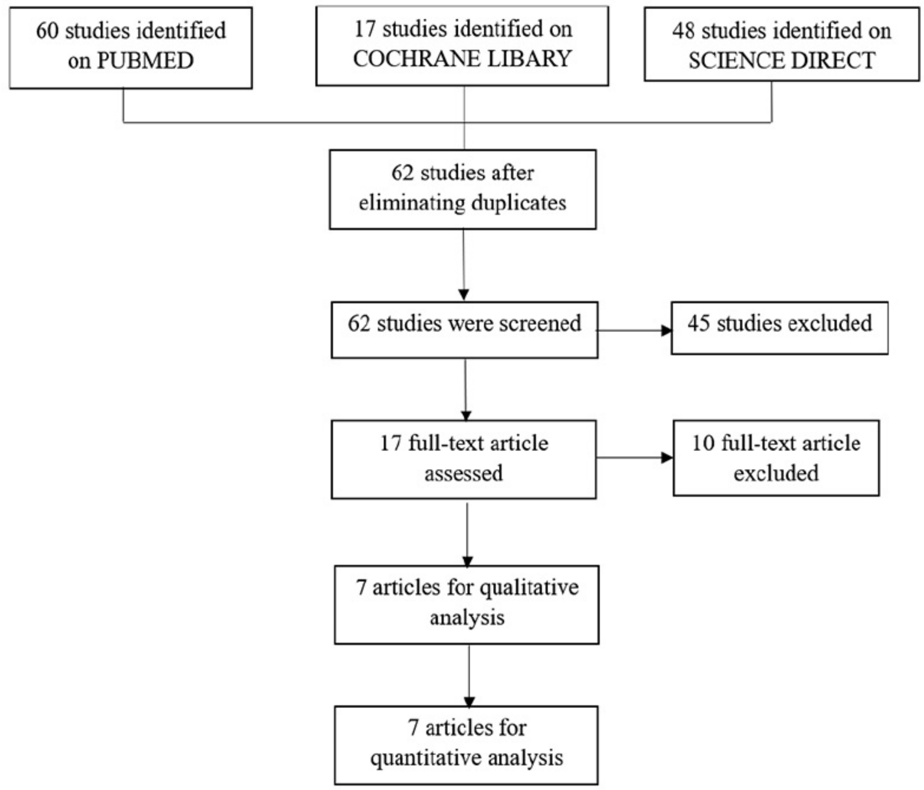

Figure 1. Study selection process

Risk of Bias Assessment

Figure 2 presents the risk of bias of each indluded studies. All 7 studies did randomization, but 4 studies[13,16,18,19] have low risk of bias in the "random sequence generation" parameter by elaborating the randomization method, and 3 studies[13,18,19] have low risk of bias in the "allocation concealment" parameter. Five studies[13,14,16,18,19] have high risk of bias on the "blinding of participants and personnel" parameter. Two studies[14,16] have high risk of bias on the "blinding of outcome assessment" parameter. The high risk of the two aforementioned parameters is due to the unique odor of ethanol that is easily recognizable by both healthcare workers and the patients, affecting the blinding process. On the "incomplete outcome data" parameter, 6 studies[13,14,16-19] have low risk of bias, while on the "selective reporting" parameter, 5 studies[13,16-19] have low risk of bias. The risk of bias assessment of the included studies is summarized in Figure 3.

The intervention of ethanol lock to the incidence of CRBSI in regular hemodialysis patients

The definition of CRBSI in each study is provided in Table 1. From 7 trials, there are 453 participants with 453 catheters included in this study. A random-effect model was used due to the significant heterogeneity between studies (P = 0.004, I^2=68%). Forest plot analysis (Figure 4) shows a significant difference in the incidence of CRBSI between the use of ethanol lock and control group (heparin lock) (RR=0.32, 95% CI 0.12-0.83, p=0.02), indicating that ethanol lock is superior in terms of reducing the incidence of CRBSI compared to heparin lock alone.

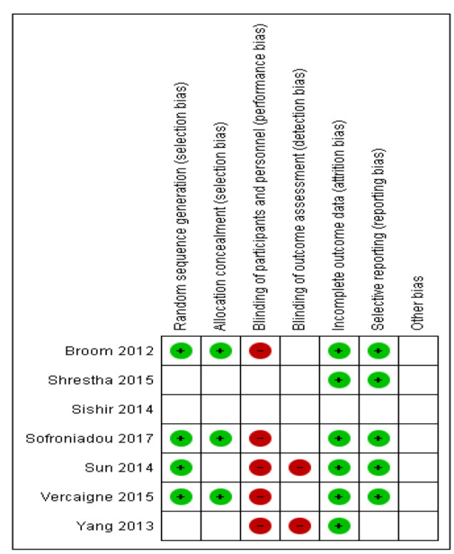

Figure 2. Risk of bias assessment of each included studies

Systemic catheter-related infections in hemodialysis patients are related to "exit-site infection." From 7 included studies, only Sofroniadou *et al.* (2017) with 11,5% incidence in the ethanol lock group and 17,6% in the control group and Broom *et al.* (2012) with 4% incidence in the

Table 1. Characteristics of included studies

Author	Country	Population	Number of patients (T/C)	Ethanol lock intervention	Control	Type of catheter	Catheter location = N (I/K)	Diagnosis of CRBSI	Diagnosis of catheter dysfunction
Sofroniadou, 2017.[19]	Greek	Hemodialysis	52/51	Ethanol 70% + unfractionated heparin 2000 U/mL in all catheter locking sessions (3x/week)	Unfractionated heparin 2000 U/mL	Non-tunneled double-lumen HD silicone catheters	Jugular=57 (31/26); subclavia= 37 (16/21); femoral=9 (5/4)	Same organism and (+) culture from both blood and catheter; no culture organism and resolved symptoms with antibiotics or catheter removal	Restricted flow at < 200 ml/min + persistent thrombosis despite additional flushing and the installation of t-plasminogen activator
Shrestha & Raut, 2015.[17]	Nepal	Hemodialysis	60/60	Ethanol 70% [1.4 ml ethanol + 0.6 ml sterile water] every 20-30 minutes before every HD sessions	Heparin 1000 IU/mL	Non-tunneled Mahurkar double-lumen polyurethane	Jugular= 60 (30/30); femoral=60 (30/30)	Same organism and (+) culture from both blood and catheter; (+) blood culture or catheter and resolve symptoms with antibiotics	Persistent flow at <200ml/min after ruling out mechanical factors and the presence of thrombosis
Broom, 2012.[14]	Australia	Hemodialysis	25/24	3mL of 70% ethanol lock (1x/week after HD) + Heparin (5000 U/ml) lock (2x/week after other HD sessions)	Heparin 5000 U/ml	Tunneled CVC	Internal jugular vein = 49 (25/24)	same type organism and (+) culture from both blood and catheter; (+) culture blood or catheter and resolve symptoms with antibiotics	Catheter blockage or reduced flow rates requiring catheter removal (failing to respond to thrombolytic therapy)
Vercaigne, 2015.[18]	Canada	Hemodialysis	20/19	2.5 mL of 30% ethanol + 4% sodium citrate (3x locking sessions/week)	Heparin 1000 U/ml	Tunneled double lumen	Internal jugular vein = 35 (20/15); External jugular vein = 4 (0/4); other site= 19 (9/10)	Same organism and (+) culture from both blood and catheter	Two consecutive dialysis sessions with blood flow of <300 mL/min for at least 50% of the session
Sishir, 2014.[15]	India	Hemodialysis	35/35	70 % ethanol lock for 20 minutes	Heparin 1000 U/ml	Non-tunneled double-lumen polyurethane catheter	No data	Same organism and (+) culture from both blood and catheter	No data
Sun, 2014.[16]	China	Hemodialysis	16/16	3.3 ml of 70% ethanol administered to the lumen and left so until the next HD session	Heparin	Tunneled CVC	Internal jugular and subclavian vein	Same organism and (+) culture from both blood and catheter	No data
Yang, 2013.[20]	China	Hemodialysis	20/20	70% ethanol administered to the lumen 1x/week	Heparin	Tunneled catheter	Internal jugular and subclavian vein	Same organism and (+) culture from both blood and catheter	No data

ethanol lock group) recorded this. The causative agent of CRBSI varies, only reported by three studies.[14,19] In Broom *et al.* (2012), isolated CRBSI organism was *Staphylococcus aureus* in the ethanol group and *Staphylococcus aureus*, *Enterobacter cloacae*, and *Staphylococcus hominis* in the control (heparin) group.[14] Sofroniadou *et al.* (2017) reported isolated *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis* (Gram-positive), and *Enterobacter cloacae* and *Klebsiella sp* (Gram-negative).[19] Shresta & Raut (2015) reported isolated CRBSI organisms including *Staphylococcus aureus*, *Enterococcus faecalis*, *Acinetobacter baumani*, *Citrobacter fruendii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[17]

The intervention of ethanol lock to the incidence of catheter dysfunction in hemodialysis patients

The definition of catheter dysfunction in each study is provided in Table 1. From 7 included trials, only 4 (311 participants, 311 catheters) evaluated catheter dysfunction related to ethanol lock. The random group model is used due to significant heterogeneity between studies ($P = 0.02$, I^2=68%). There is no statistically significant difference in catheter dysfunction in the included studies (RR=0.75, 95% CI 0.23-2.40, p=0.63), indicating that ethanol lock does not affect catheter dysfunction conventional heparin lock. Several inclusion studies reported side effects related to ethanol lock. According to Sofroniadou *et al.* (2017), 6 participants in the ethanol lock group experienced short-term perioral dysaesthesia or metallic taste.[19] Sun (2014) reported 3 participants experiencing side effects, each with flushing, bleeding, bad smell on the ethanol lock group, and 4 bleedings in the control group.[16] Yang *et al.* (2013) reported 1 incidence of dizziness in the ethanol group.[20] Vercaigne *et al.* (2015) reported 3 adverse events suspected to be related to the use of ethanol lock, including axillo-femoral graft occlusion, gastrointestinal bleeding, and septic episode. However, the gastrointestinal bleeding occurred in an anemic patient with a benign ulcer in the stomach antrum. The patient with sepsis had preexisting pedal gangrene and up for amputation right before the study was conducted thus obscuring the effect of an ethanol lock to this adverse event.[18]

DISCUSSION

Analysis of 7 studies found that the risk of CRBSI in ethanol lock was only 32% compared to heparin lock. Therefore ethanol lock significantly reduced the incidence of CRBSI in HD patients by 68%. These findings are similar and in line with the meta-analysis by Zhang P *et al.* (2018), with a decrease in the incidence of CRBSI about 34%. However, the population in the meta-analysis was diverse (not focused on only HD patients).[21] As the secondary outcome, the effect of ethanol lock on the incidence of catheter dysfunction has the same level as heparin lock, which is consistent with the meta-analysis by Zhang J *et al.* (2019), who also evaluated ethanol but in a more diverse population.[22]

There are two ways for pathogen micro-organisms to enter the bloodstream and cause CRB. First, the extraluminal way describes organism contact on the

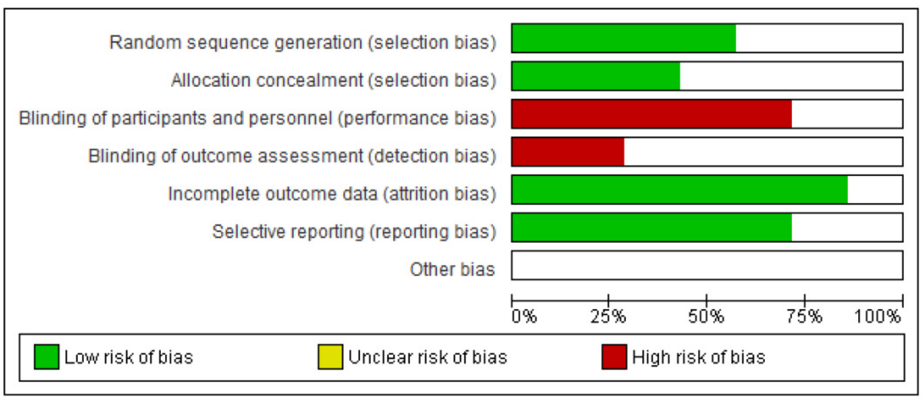

Figure 3. Summary of risk of bias assessment based on each parameter

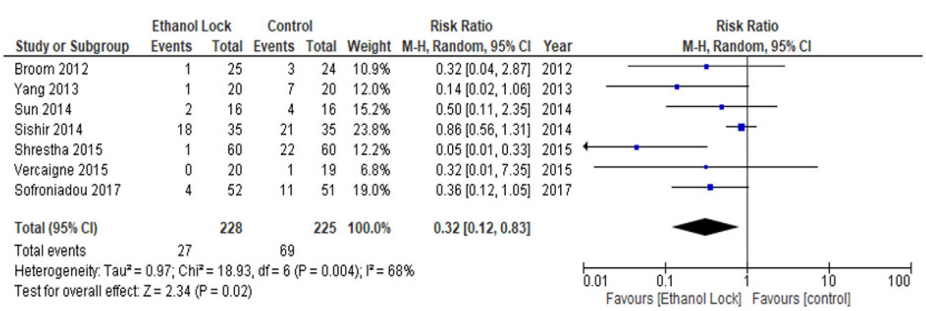

Figure 4. Forest plot of the effect of ethanol lock in the incidence of CRBSI in regular hemodialysis patients

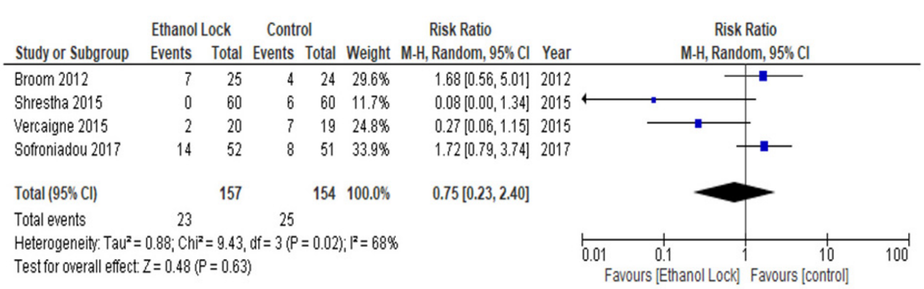

Figure 5. Forest plot of the effect of ethanol lock and catheter dysfunction in regular hemodialysis patients

skin with the catheter's outer surface, which migrates downward following the outer canal of the catheter to the tip where the hematogenous spread occurs. Second, the intraluminal way involves the transfer of organisms via the contact from an individual's (usually a healthcare worker) hand accessing the CVC or the patient's skin/surrounding clothing to the hub or catheter cap, resulting in contamination of the internal catheter surface. If the treatment of the exit site after insertion is done aseptically and properly, exit site infection can be minimized. However, the possibility of organism entry via the intraluminal route remains throughout catheter attachment. Intraluminal route infection begins within 24 hours of catheter insertion. Following adhesion, these micro-organisms form a structure called biofilms. A perfect biofilm consists of micro-organisms protected by a self-secreted matrix of exopolysaccharides. Common organisms found in biofilms include *Staphylococcus*, *Candida*, and *Pseudomonas*. The presence of these biofilms facilitates ongoing and recurrent infection in patients with vascular catheters and the spread of hematogenous pathogenic micro-organisms. Therefore, the management of patients with CRBSI involves preventing micro-organisms attachment to the catheter and overcoming pathogenic biofilms by targeting the intraluminal catheter entry route. Moreover, heparin's current conventional lock is reported to play a role in forming pathogenic biofilms.[7,10]

Ethanol (30% to 70% concentration) possesses bactericidal properties and other advantages, namely inexpensive, ability to reduce biofilm formation, has no resistance to agents, has a broad spectrum of antimicrobial and antifungal properties.[6] Ethanol 70% works by damaging protein structures, unlike antibiotics, which may explain how ethanol reduces the risk of resistance.[23] The potency of ethanol as a catheter lock to reduce the incidence of systemic infection associated with vascular access catheter insertion has been evaluated from *in vitro* studies. A study by Alonso *et al.* in 2018 assessed the lowest effective concentration of ethanol in inhibiting biofilm formation in the catheter. The 40% ethanol reportedly does not affect the 60 IU heparin action, in which heparin is known as the standard vascular access catheter lock. A follow-up study was carried out on the pathological strain of CRBSI that was isolated directly from the patient from these results. Alonso *et al.* 2019, in their other study, evaluated a low concentration of ethanol lock of 40%-heparin 60 IU against clinical micro-organism strains (isolated from hospital CRBSI patients) with *in vitro* study models as a follow-up from previous studies using laboratory pathogenic strains. The result was that a low ethanol concentration of 40% for 72 hours reduces the metabolic activity of CRBSI organisms by 83% (no significant difference with that of 70% ethanol) and can be combined with heparin without reducing heparin activity which requires 24 hours of locking or more. In this study, it was also found that the composition of the ethanol solution was also efficient in reducing the biofilm mass in CRBSI by 50% of the clinical strain. However, unfavorable results were obtained in the regrowth inhibition test after 72 hours of locking. According to the study, micro-organisms switch to a viable but non-culturable state (metabolically inactive) due to an unfavorable environment.[11]

Apart from *in vitro* studies, the clinical use of ethanol has also been studied by several other studies. A review study on the use of 70% ethanol as a catheter locking in home parenteral nutrition (HPN) patients for the prevention of CRBSI showed good results, where several studies reported a decrease in the CRBSI rate from 8.3 to 2.7 per 1000 catheter days, and retrospective studies on 31 patients showed a decrease of 10.1 to 2.9 per 1000 catheter days.[23] A retrospective study by Kubiak *et al.* in 2014 on pediatric patients who received ethanol lock therapy with CVC catheter use stated that CVC in pediatric patients is often due to indications of chemotherapy and total parenteral nutrition. Thirty-five out of the 45 cases of CRBSI (78%) showed improvement in symptoms, and blood cultures became sterile after applying ethanol lock therapy for 4 to 12 hours daily for five days.[8] The advantages of ethanol lock in this retrospective clinical study in reducing CRBSI are in line with *in vitro* studies from Shrestha *et al.* at ≥30% concentration, in which ethanol is superior to several antibiotics (vancomycin, ciprofloxacin, minocycline, and rifampicin), with the ability of microbial eradication around 3,6 – 3.9 log units at 2, 4, and 24 hours. At ≥35% concentration, ethanol has been shown to reduce the metabolic activity of matured *Candida albicans* biofilms by > 99%. The weakness of this retrospective study is the subjective observation of medical personnel treating patients with catheters and ethanol lock therapy. The result that there were no reports of side effects associated with ethanol lock can be explained by the minimal amount of ethanol that reached the systemic circulation in this study protocol. Most of it was aspirated after the dwelling period. Therefore, the ethanol lock solution administered in the CVC should be aspirated instead of flushed into the systemic circulation.[17]

Aside from the need for parenteral nutrition and chemotherapy, long-term vascular access catheter in hemodialysis patients deserves attention due to the large population in need. Merikhi *et al.* (2019) evaluated the use of ethanol lock in pediatric hemodialysis patients suffering from CKD related to catheter-related infection compared to 10 mg clindamycin lock. Both regimens were combined with heparin. The antibiotic lock was administered 3x/week while ethanol was given 1x/week while the remaining sessions utilized heparin lock (2x/week). This resulted in decreased catheter site infection to only 12% in the ethanol lock group than the initial 44% in the antibiotic lock group. This study also observed that there was no protein precipitate sediment formation in the ethanol-heparin lock combination group. This indicates that the addition of heparin to ethanol as catheter lock can decrease the incidence of catheter thrombosis as a side effect of protein precipitation.[24]

There are several possible side effects of ethanol lock, both to the catheter and to the body. Catheter-wise, ethanol is associated with catheter thrombosis and the mechanical integrity of the catheter. Catheter thrombosis is associated with protein precipitate that causes catheter occlusion, while ethanol is associated with reduced material integrity. Studies revealed that protein precipitate starts forming in ethanol concentration of 28% or higher, but no precipitate was observed in heparin lock. This leads to the combined use of ethanol and heparin to minimize serum protein precipitate in catheters.[25] The use of a higher concentration of ethanol (70%) is associated with its effect on mechanical integrity. There was no significant difference in catheter integrity (stress/strain test and elastic modulus) in 70% ethanol and heparin after 26 weeks in either silicon or carbothane catheter group.[12] However, it is worth noting that this was an *in vitro* study using catheters from one producer. Therefore, ethanol is advisably used only with alcohol (ethanol)-compatible catheters made of carbothane or silicon. Presumed systemic effects of ethanol including abnormal liver function test, mainly elevated transaminases, reports of headache, nausea, dizziness, and fatigue. These reports are more commonly found in studies that flushed, instead of aspirated, ethanol lock.[7,26] From here, several means to minimize the adverse effect of ethanol lock can be inferred:

a) Only use ethanol as a lock for producers-approved catheters
b) Use the minimum effective concentration (30%-40% is suggested) with minimum dwell time to preserve the integrity of the catheter, and use other additional agents (such as heparin) to prevent intraluminal obstruction. Ethanol is advisably aspirated instead of flushed following the end of dwell time. Observe for signs and symptoms of alcohol intoxication.[6]

CDC and Infectious Diseases Society of America (IDSA) do not recommend routine use of antimicrobial lock-in hemodialysis patients with CVC. Antimicrobial locks are recommended for patients with a history of recurrent CRBSI due to concerns of potential antimicrobial resistance.[7,12] The European Best Practices Report, however, concluded that the effectiveness of antimicrobial lock to reduce CRBSI overcomes the risk and adverse effects, thus commending its use as a prophylactic in all ESRD patients with CVC.[12] Meanwhile, ethanol may be an alternative as an additional catheter locking agent due to its potency in reducing catheter-related systemic infection and near-zero risk of resistance up to this day.

A shortcoming of this study is that there are varied methods and interventions, notably the concentration of the ethanol and ethanol alone or in combination with other substances in each included study, posing as a potential bias of the analytic result. However, through the results of this study, ethanol as a non-antibiotic antimicrobial agent will be more convincing as a means to reduce CRBSI and is deemed safe for clinical practice.

CONCLUSION

Ethanol, both as an additional regimen to the standard heparin lock or as an individual catheter locking solution, is a potential prophylactic agent in preventing and reducing the incidence of catheter-related bloodstream infection (CRBSI) in hemodialysis patients with vascular access in the form of either temporary or permanent tunneled catheter. Ethanol application as catheter lock effect on catheter dysfunction has the same level as standard heparin locks in general, therefore its effect on catheter dysfunction can be ignored. The key application of ethanol as therapy in CRBSI cases is clinically concerned with several factors, namely the concentration of ethanol, the method of locking (flushing or aspiration), the frequency of locking, the length of time of locking, and the combination with heparin. The authors assume that a higher concentration of ethanol used as a catheter lock will result in shorter required locking/dwelling time and less frequent usage, and vice versa. Therefore, further clinical studies are needed to determine the relationship between concentration, locking time, and usage frequency of ethanol lock.

CONFLICT OF INTEREST

There was no conflict of interest to disclose.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTION

All of the authors are equally contributed to the study

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