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RESEARCH ARTICLE

COMBATING HEMODIALYSIS CATHETER-RELATED INFECTION USING AN ANTIBIOTIC LOCK, ACASE-CONTROL STUDY, AT KING FAHD HOSPITAL OF THE UNIVERSITY, SAUDI ARABIA

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Abstract

Background: Catheter-related infections (CRI) in hemodialysis patients are very common complications with devastating consequences if not managed appropriately, as most of the morbidity and mortality among these patients are caused by bacteremia related to hemodialysis. Hence, safety issues exist to restrict the spread of infections among this group of patients. A prophylactic technique that is worth of much discussion is the use of antimicrobial lock solutions (ALS). Several studies have been conducted in this area. Yet, there is no consensus recommendation in this regarding. Hence, the purpose of our study is to examine the efficacy of ALS for prevention of CRI in patients undergoing HD. Methodology:

Methods:A total of 86 TCC in 69 HD patients were enrolled at the time of catheter insertion for delivering HD. Patients were randomized into two groups: Group I (36 patients-39 insertions) included TCC with antibiotic-lock therapy and Group II (33 patients-47 insertions) with routine TCC management. Infection-free catheter survival of both groups was evaluated and compared at the end of the 7-month study period.

Results:A total of 67 TCC-related infections were detected, with an incidence rate of 8.79/1000 dialysis sessions (ds). Out of these infections, 50 belonged to patients in group II with an incidence rate of 12.88/1000 ds, and 17 in patients of group I with an incidence rate of 4.51/1000 ds ($p<0.001$) (Table 3). The bacteremia rate was 5.14/1000 ds in patients of group II and only 0.63/1000 ds in patients of group I ($p<0.001$). Clinical sepsis occurred in 19 (28.4%) of the 67 TCC infections. Clinical sepsis rate was significantly lower in patients of group I (0.61/1000ds) compared with 4.12/1000 ds in group II patients ($p<0.005$).

Conclusion: TCC lock with vancomycin and gentamycin appears to be highly effective strategy for the reduction of morbidity, and potentially mortality and costs, associated with TCC-related bacterial infections in HD patients. In this study, this protocol was free of side effects.

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Introduction:-

Patients undergoing hemodialysis (HD) are at higher risk of infections, which are closely associated with adverse events among this group of patients. Compared to the general population, the annual mortality due to bacteremia is 100-300 times greater in hemodialysis patients. Even if other factors, including age, race, gender, diabetes, and data errors are taken into account, mortality due to bacteremia remains 50 times greater (1, 2).Thus, infections are believed to be the leading cause of morbidity, and the second commonest cause of mortality in patients undergoing hemodialysis (3).

The rate of HD-related infection varies as per the access of HD. A study conducted in Greece, reported that most of the bacteremia episodes were associated with the central venous catheter (CVC), and that CVC-related risk of infection is 10 times higher than the arteriovenous fistula infections (4). Another study reported an incidence ratio for blood-stream infection based on the access of HD to be 1.84 (95% CI:1.06-3.16) with arteriovenous graft access (P=.029), 4.85 (95% CI:3.0-7.85) with permanent central venous catheter access (P<.001), and 14.88 (95% CI:10.18-22.20) with temporary catheter access (P <.001) (5). In a more recent study, the authors focused more on CVC-related infections and found an incidence of 36.2% (34 out of 94 patients on HD), with 152 CVC procedures. The analysis revealed that 16.6 per 1000 CVC-days incidence of CVC-related infections, and 10.8 per 1000 CVC-days incidence of CVC related-bloodstream infections (6).

Several risk factors were believed to be contributing to HD related infections. However, the published articles reported some contradicting results, where some authors believed that some of these factors are independent of the dialysis procedure. One of these studies concluded that diabetes mellitus was the main risk factors for infection followed by the duration of catheterization (6). However, another study believes that hemodialysis related infection was independent of the CRP-value, the presence of diabetes, or the presence of immunosuppression. Catheter-related infections were observed by other researchers to be more frequent in patients with MRSA-carriage, previous catheter-related infections, and bacteremia or bacteriuria in 3 months before kidney implantation (7). However, the same authors believed that the site of catheter insertion and duration of catheterization were related to infections in most cases. Moreover, another study concluded that the main risk factor for developing bacteremia dialysis access, as the incidence was higher in HD catheter using patients compared to arteriovenous (AV) access group, followed by previous hospitalization as the second risk factor for developing such a complication (8).

Central venous catheters (CVC), arterial catheters and dialysis catheters are inserted in 3 out of 4 critically ill patients' intensive care unit (ICU). Complications included local insertion site complications, infections and thrombosis (9, 10) Therefore, safety issues exist to restrict the spread of infections among hemodialysis patients.

Antimicrobial lock solutions (ALS) is a prophylactic technique that is worth of much discussion for the prevention and treatment of catheter-related bloodstream infections. It has been examined in several trials, but no consensus is available for clinical practice. In general, antibiotic lock solutions combine a highly concentrated antibiotic (100–1,000 times planktonic MIC) with an anticoagulant to allow for local instillation into the cath- eter lumen. The solution is allowed to dwell or is "locked" while the CVC is not in use to prevent colonization or sterilize a previously infected catheter. ALT is often utilized in clinical practice in a prophylactic modality to prevent luminal colonization and subsequent Catheter-related bloodstream infection (CRBSI). This practice has demonstrated significant benefit in hemodialysis-dependent patients and those with indwelling CVC for intravenous (IV) chemotherapy and total parenteral nutrition (TPN) (11,12,13).

Methods:-

Study Design:

We prospectively studied all hemodialysis patients who had Tunneled, Central Catheter (TCC) at King Fahd Hospital of the University, at Al-Khobar, Saudi Arabia for TCC-related infections over a 7 month period (July 2020 - January 2021). The total number of dialysis sessions were recorded on a daily basis and randomized into two groups: group I (39 patients/41 TCC insertions) who had antibiotic-lock protocol, and group II (36 patients/46 TCC insertions) with routine TCC placement and management. Our antibiotic-lock protocol consisted of a mixture of vancomycin hydrochloride 25 mg/ml, gentamycin sulphate 40 mg/ml, and heparin 5000 U/ml; a total of 1.5-1.75 ml in the venous side and 1.25-1.5 ml in the arterial side of the TCC was instilled at the end of each dialysis session and withdrawn immediately before the next dialysis session. Heparin at this concentration was compatible with our antibiotic mixture. At each dialysis session, patients were evaluated by the nephrologist and a trained hemodialysis

nurse for evidence of TCC-related infection. Cultures were obtained from the catheter exit site and from patients' blood each time. The presence of infection was recorded and tabulated by a trained nurse under the supervision of the nephrologist. Blood samples were collected from a peripheral vein at the beginning of each dialysis session, and both vancomycin and gentamycin blood levels were measured.

Case Definitions:
The CDC definitions for infections with or without bacteremia were used(14). Blood for cultures was obtained by drawing blood from the TCC arterial and venous lines as well as peripheral blood samples. Positive cultures reported by the clinical microbiology laboratory were reviewed daily by staff from the Hospital's Infection Control Unit.

Microbiological Tests:
Swabs from TCC site were inoculated onto agar media using standard techniques (15). Blood cultures were performed for aerobic and anaerobic organisms according to established methods (16). Bacteria were identified using Microscan (Microscan system, Renton, WA, USA) system.

TCC Care:
Catheters were inserted by one team preferentially in the right internal jugular vein, followed by the left internal jugular vein and then the femoral veins whenever internal jugular veins are inaccessible. The catheter exit site was cleaned with a topical iodine solution at the initiation and termination of each dialysis session and covered by dry sterile gauze during the interdialytic period. No topical or systemic antibiotic prophylaxis was used in the catheter-dependent dialysis patients. Surgical and radiological procedures were carried out under complete aseptic precautions.

Data Analysis:
Infection rates were calculated in both groups for total, blood stream, clinical sepsis, and TCC-exit site infection. Data analysis was performed according to the CDC National Infection Surveillance System (17). Statistical analysis was performed with Epi Info, 2000, USD, Snellville, USA).

Results:-

A total number of 81 TCC were inserted, among a total of 63 patients who had dialysis during the past seven months. Regarding nationalities and genders, 93.3% were Saudi, and 60.3% were males. Table 1 shows the detailed breakdown of the patients included. Table 2 shows a total of 6372 dialysis sessions that were conducted through the time period, with a monthly mean of 910 sessions. Moreover, 57 TCC-related infections were recorded and had an incidence of 8.9 per 1000 dialysis sessions (ds). 57 TCC-related infections were recorded. 30/63 cases were among G2 patients (incidence rate of 13.11 per 1000 ds), On the other hand, 33/63 were among G1 (incidence rate of 4.54 per 1000 ds) Table 3. Complicated bacteremia was identified in 18/63 cases (28.57%), 4.88 per 1000 ds in among G2, and only 0.65 per 1000 ds among G1 patients ($p<0.001$). Also, clinical sepsis rate was 4.27 per 1000 ds among G2 patients, which is significantly higher than patients in G1 where the rate was 0.65 per 1000 ds ($p<0.001$). Regarding access site-related infections, the rate was 3.96 per 1000 ds among G2 patients, and 3.24 per 1000 ds among G1 patients, however the difference in rate in this context was not shown to have a significance ($p>0.05$). Vancomycin hydrochloride levels of <0.5 mcg per ml was found in 7.7% of patients in G1, however in 92.3% of patients the level was undetectable. On the other hand, gentamicin sulfate levels of <0.1 mcg per ml were found in 5.2% among G1 patients but were generally undetectable in 94.8% of patients in the same group. Table 4 shows a detailed breakdown regarding the organisms that were isolated from either the access site, or from the blood, and the total number of organisms that were isolated. Generally, 72% of the isolated organisms were gram-positive cocci, on the other hand only 28% were found to be gram-negative bacilli. In Figure 1 the prevalence of infective organisms is shown. In 93.2% of patients, the TCC was removed and was followed by a total eradication of the infection. However, in the remaining 6.8% of the patients, prolonged IV antibiotic use was a necessity.

Discussion:-

One of the most important problems associated with catheter insertion is the related infections. It has been estimated that annually 250,000 to 500,000 blood infections occur due to the insertion of central venous catheter (18). High mortality, High hospital costs and longer hospitalization are among the related problems (19, 20).

Different studies demonstrated the inability of antibiotics to minimize the risk of exposing patients to recurrent infection and they attributed this to failure or ineffective central catheter sterilization (17, 21, 22). In addition, it was shown that systemically administered antibiotics failed to sterilize the catheter lumen due to insufficient diffusion of antibiotic into the catheter lumen (16, 17, 21) Consequently, an attention has turned to the antibiotic lock technique, aka intraluminal therapy; a therapeutic technique that allows the in-situ prophylaxis against TCC infections aiming at improving TCC outcomes along with minimizing the adverse effects of systemic antibiotics. The intraluminal antibiotic therapy was accomplished by the instillation of antibiotic solution with certain volume and concentration into the TCC lumen to avoid spill out into the systemic circulation. This "antibiotic lock" is kept in place during the interdialytic daysbefore removal at the beginning of the next dialysis session, and to be replaced at the end dialysis.

Dialysis catheter-related infection may be caused by several bacteria. The most common pathogens causing dialysis catheter-related infection are Staphylococcus aureus and Staphylococcus epidermidis, and prevalence of antibiotic resistance is significantly high among them (22-25). Despite the provision of various guidelines for catheter use and the necessary care to maintain its safety and sterility, the rate of catheter infection has increased in the last decades (24, 26,27). Biofilm formation in the inner layer of the catheters, central venous infections, and septicemia are among important factors that have been associated with increased mortality and morbidity according to previous studies (28-30). To prevent infection, antibiotics can be used as combination of one or more antibiotic with specific dosage with an anticoagulant within the catheter lumen; vancomycin and gentamicin has a wide use (31). Results of various studies have shown that the success rate of this method is modest, and more studies are needed to more clearly examine the role of new types of antibiotics in preventing infection (32).

Studies on the effect of antibiotic lock on reducing the rate of catheter-related infections have mostly reported the benefits and effectiveness of this technique; however, one of the most important issues in this regard is antibiotic resistance which has been raised in various studies. Landry et al. used gentamicin-heparin lock in their study and stated that resistance to gentamicin increased over a period of 6 months (33). They suggested that the use of a non-antibiotic catheter lock may result in decreased catheter-related infection. In the study of Venditto et al., increased Enterobacteriaceae resistance to gentamicin is noted; however, staphylococcus resistance was reported to be insignificant in this study (34). Also, in other studies, the antibiotic resistance was low (35, 36). The reason for these differences may be the difference in the dosage of antibiotics and the antibiotics combination with other solutions such as the use of a lock consisting of heparin, gentamicin and citrate. Our antibiotic-lock protocol contained a combination of vancomycin, gentamycin and heparin; the high concentration of heparin (3500-10,000 U/ml) does not interact with a broad range of antibiotics including gentamycin and vancomycin. Our results in patients who were managed with the antibiotic lock therapy revealed significant decrease of the overall TCC-related infections over the study period.The overall TCC-related infections decreased significantly over the 7-month study period from 12.92/1000 dialysis sessions in patients with the routine TCC care, to 4.51/1000 dialysis sessions in those who received our protocol of the antibiotic lock therapy. The rates of bacteremia as well as clinical sepsis were significantly less in the latter ($p< 0.001$ in either case). In addition, it was beneficial in minimizing more invasive procedures such as systemic antibiotic therapy, TCC removal, and other surgical maneuvers.Further studies are needed to compare paraclinical parameters and their changes after the introduction of catheter-related infections prevention techniques, so that more precise results can be obtained.Although our patients' population was not large, compared with previous reports, our study was one of the pioneers to validate the value of utilizing the combination of vancomycin and gentamycin in the antibiotic lock technique as an effective and safe prophylactic measure against TCC-related infections.

Conclusion:-

TCC lock with vancomycin and gentamycinappears to be an effective strategy for the reduction of morbidity, and potential mortality, associated with TCC-related bacterial infections in HD patients. In this study, this protocol was free of side effects. The implications of our study extend beyond renal units, as tunneled central catheters are now widely used in other specialties.

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Table 1:- Breakdown of patients studied.

Items (unit)	Group I n = 33	Group II n = 30	**p** value
Age, years (mean)	48.3+11.5	44.7+7.4	>0.05
Sex (female/male)	13/20	12/18	>0.05
Weight at baseline, mean (kg)	77.5+6.1	69.8+7.7	>0.05
BUN mg/dl (mean)	79.9+12.3	82.2+11.8	>0.05
Creatinine (mean)	12.6+6.3	11.9+8.0	>0.05
Hematocrit (mean)	27.4+2.4	25.8+3.2	>0.05
DM* (%)	18.2 (n=6)	23.3 (n=7)	>0.05
HPN** (%)	78.8 (n=26)	73.3 (n=22)	>0.05
Site of TCC© (IJV®/Femoral)	29/4	27/3	>0.05

* Diabetes mellitus, ** Hypertension, ©Tunneled-central-catheter, ® Internal jugular vein.

Table 2:- Number of dialysis sessions in the two groups of patients.

Group	**No**
Group I (with antibiotic lock)	3091
Group II (without antibiotic lock)	3281
Total	**6372**

Table 3:- Data summary of TCC infections.

	Group I (37 insertions)		Group II (44 insertions)		**p**
	No	Rate*	No	Rate	
Bacteremia	2	0.65	16	4.88	<0.001
Clinical sepsis	2	0.65	14	4.27	<0.001
Access site	10	3.24	13	3.96	>0.05
Total	14	4.54	43	13.11	<0.001

***Per 1000 dialysis sessions**

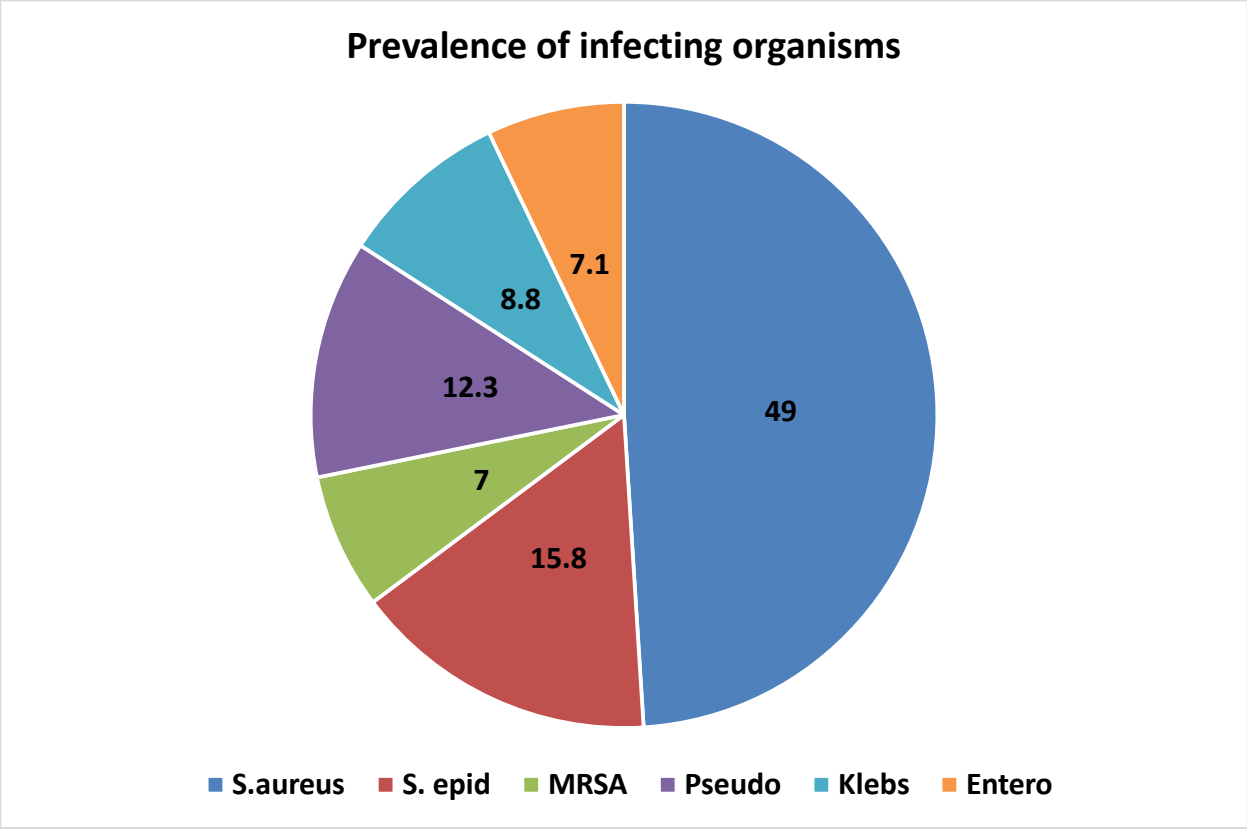
Table 4:- Breakdown of organisms isolated from access sites and blood.

Organism	Access site		Blood		**Total**	
	No	(%)	No	(%)	No	(%)
Staph. epidermidis	11	(47.8)	17	(50.0)	28	(49.1)

Staph. aureus	5	(21.7)	4	(11.8)	9	(15.8)
MRSA*	2	(8.7)	2	(5.9)	4	(7.0)
Pseudomonas aeruginosa	2	(8.7)	5	(14.7)	7	(12.3)
Klebsiella pneumoniae	2	(8.7)	3	(8.8)	5	(8.8)
Enterobacter cloacae	1	(4.4)	3	(8.8)	4	(7.0)
Total	23	(100)	34	(100)	57	(100)

*MRSA: Methicillin-resistant Staphylococcus aureus.

Legend of figure-1
Prevalence of TCC-related infecting organisms. S. epid: Staphylococcus epidermidis; MRSA: methicillin-resistant Staphylococcus aureus; S. aureus: Staphylococcus aureus; Pseudo: Pseudomonas aeruginosa; Klebsiella: Klebsiella pneumoniae; Entero: Enterobacter cloacae.



S. aureus: Staphylococcus aureus, S. epid: Staphylococcus epidermidis, MRSA: Methicillin resistant Staph aureus, Pseudo: Pseudomonas aeruginosa, Kleb: Klebsiella species, Entero: Enterobacter species

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