LAPORAN AKHIR
IRPA /USM JANGKA PENDEK

PERANAN UBAT SALAP MUPIROCIN SEBAGAI PENCEGAH JANGKITAN KUMAN PADA KATETER DIKALANGAN PESAKIT HEMODIALISIS .

ROLE OF TOPICAL MUPIROCIN OINTMENT AS A PROPHYLAXIS IN CATHETER RELATED INFECTION IN HAEMODIALYSIS PATIENTS.

OLEH

DR KAMALIAH BT MOHD DAUD
JABATAN PERUBATAN

Semua laporan kemajuan dan laporan akhir yang dikemukakan kepada Bahagian Penyelidikan dan Pembangunan perlu terlebih dahulu disampaikan untuk penelitian dan perakuan Jawatankuasa Penyelidikan di Pusat Pengajian.

USM JP-06

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2) **Pusat Pengajian/Pusat/Unit:** PPSP

3) **Tajuk Projek:** Peranan ubat salap mupirocin sebagai pencegah jangkitan kuman pada kateter dikalangan pesakit hemodialisis

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ABSTRAK

Pemasangan kateter vena pusat(KVP) adalah teknik yang selalu digunakan untuk memberikan rawatan hemodialisis kepada pesakit-pesakit yang mengalami kegagalan buah pinggang. Walau bagaimanapun kepenggunaannya juga membawa beberapa masalah yang serius seperti jangkitan bakteria dan kematian. KVP juga membawa risiko jangkitan Staphylococcus. Mupirocin adalah antibiotik yang terhasil secara semulajadi yang aktif terhadap jangkitan Staphylococcus termasuk rintang meticilin (MRSA) serta strain yang menghasilkan beta laktam.

Satu kajian prospektif telah dijalankan terhadap 28 orang pesakit hemodialisis untuk menganalisa peranan mupirocin sebagai pencegah jangkitan kateter vena pusat. Tigabelas pesakit telah menerima desinfeksi povidon iodine pada pangkal KVP (kumpulan kawalan) dan 15 pesakit menerima rawatan yang sama diikuti dengan penggunaan salap mupirocin 2% sejurus selepas kateter dimasukkan dan pada akhir setiap rawatan dialisis. Kesemua pesakit diawasi sehingga kateter dikeluarkan dan pemantauan dilakukan untuk mengetahui perkembangan jangkitan berkaitan dengan kateter.

Kadar jangkitan didapati adalah ketara lebih rendah pada kumpulan mupirocin (6.7 % berbanding 38.4 %, $P < 0.05$). Bakteremia Staphylococcus aureus dan MRSA telah diperhatikan berlaku pada 4 pesakit kumpulan kawalan (30.7 %) dan ianya melibatkan 3 kematian berkaitan dengan jangkitan. Ini tidak berlaku pada kumpulan mupirocin. Nisbah bahaya untuk mendapat jangkitan berkaitan dengan kateter adalah 7.7 kali lebih kepada pesakit yang tidak menerima mupirocin.

Kesimpulannya penggunaan salap mupirocin pada bahagian pangkal kateter dapat mengurangkan risiko jangkitan berhubung dengan kateter terutamanya septisimia Staphylococcus aureus pada pesakit hemodialisis.

F

ABSTRACT

Central venous catheterization (CVC) is a common technique to establish rapid and temporary access for the delivery of haemodialysis in patients with renal failure. However its usage also carry tremendous problems such as infection, sepsis and even death. CVC is a known risk factor for Staphylococcus infection and bacteraemia. Mupirocin is a naturally occurring antibiotic which is active against Staphylococcus aureus including methicillin resistant and beta lactamase producing strains.

A randomized prospective trial was conducted to assess the role of mupirocin ointment as a prophylaxis in catheter related infection in 28 haemodialysis patients. Of these 13 received skin disinfection at CVC insertion site with povidone iodine (control group) and 15 received the same treatment followed by topical application of 2% mupirocin ointment at the cannula site immediately following catheter placement and at the end of each dialysis session. Patients were followed up until catheter removal and were monitored for the development of catheter related infection (CRI).

The proportion of CRI in mupirocin group was significantly lower than control (6.7% vs. 38.4%, $P < 0.05$). Staphylococcus aureus and MRSA bacteraemia was observed in 4 patients (30.7%) in control group and 3 of them died related to sepsis. None of these was observed in the mupirocin group. The hazard ratio of developing catheter related infection was 7.7 times greater in patients not receiving mupirocin.

As a conclusion, topical mupirocin application at the catheter exit site significantly reduced the risk of catheter related infection especially Staphylococcus aureus septicaemia in haemodialysis patients.

Semua laporan kemajuan dan laporan akhir yang dikemukakan kepada Bahagian Penyelidikan dan Pembangunan perlu terlebih dahulu disampaikan untuk penelitian dan perakuan Jawatankuasa Penyelidikan di Pusat Pengajian.

USM R&D/JP-04

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Tajuk Projek: "Peranan Ubat Salap Mupirocin Sebagai Pencegah Jangkitan Kuman Pada Kateter Dikalangan Pesakit Hemodialisis" / "Role of Topical Mupirocin Ointment As A Prophylaxis In Catheter Related Infection In Haemodialysis Patients"

Tajuk Program:

Tarikh Mula: 01 Julai 1999

Nama Penyelidik Utama: Dr Kamaliah Bt Mohd Daud (No k/p : 640504-11-5166)
(*berserta No. K/P*)

Nama Penyelidik Lain: Dr Mohd Zaki Salleh dan Dr Azeril Haris Yafee Amar
(*berserta No. K/P*) (550908-07-5069) (690430-03-5141)

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Penggunaan ubat salap mupirocin dapat mengurangkan kadar jangkitan kuman pada kateter vena pusat dikalangan pesakit hemodialisis dengan kos yang rendah tetapi berkesan

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☐ **Memperbaiki/meningkatkan produk/proses/teknik yang <u>sedia ada</u>**
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D. KOMERSIALISASI

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(*Klien dan jenis perundingan*)

(1) _____

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(3) _____

(4) _____

F. PATEN/SIJIL INOVASI UTILITI

(*Nyatakan nombor dan tarikh pendaftaran paten. Sekiranya paten/sijil inovasi utiliti telah dipohon tetapi masih belum didaftarkan, sila berikan nombor dan tarikh fail paten*).

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(2) _____

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G. PENERBITAN HASIL DARIPADA PROJEK

(i) LAPORAN/KERTAS PERSIDANGAN ATAU SEMINAR

(1) Telah dibentangkan dalam bentuk poster semasa "13th Asian Colloquium in Nephrology" pada 23-25 November 2000 di Bali, Indonesia.

(2) Telah diterima untuk dibentangkan (oral/poster) semasa "The 46th Annual Meeting of Japanese Society for Dialysis Therapy" pada 22 – 24 Jun 2001 di Osaka, Jepun.

(3) Akan dibentangkan dalam bentuk oral pada 1st Asean Conference on Medical Sciences pada 18 – 21 May 2001 di Pusat Pengajian Sains Perubatan , Universiti Sains Malaysia.

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D. KOMERSIALISASI

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Nama Klien: (1) _____

(2) _____

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☐ Berpotensi untuk dikomersialkan.
(Nyatakan jenis klien yang mungkin berminat)

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E. PERKHIDMATAN PERUNDINGAN BERBANGKIT DARIPADA PROJEK

(*Klien dan jenis perundingan*)

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I. **SUMBANGAN KEWANGAN DARI PIHAK LUAR**
(Nyatakan nama agensi dan nilai atau peralatan yang telah diberi)

(1) _____

(2) _____

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J. **PELAJAR IJAZAH LANJUTAN**
(Nyatakan jumlah yang telah dilatih di dalam bidang berkaitan dan sama ada diperingkat sarjana atau Ph.D).

	Nama Pelajar
Sarjana	Dr Azril Haris Yafee b. Amar
Ph.D	

K. **MAKLUMAT LAIN YANG BERKAITAN**

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I. **SUMBANGAN KEWANGAN DARI PIHAK LUAR**
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Ph.D	

K. **MAKLUMAT LAIN YANG BERKAITAN**

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Role of Topical Mupirocin Ointment As A Prophylaxis in Catheter Related Infection in Haemodialysis Patients

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Keywords

Catheter related infection, haemodialysis, mupirocin.

ABSTRACT

Central venous catheterization (CVC) is a common technique to establish rapid and temporary access for the delivery of haemodialysis in patients with renal failure. However its usage also carry tremendous problems such as infection, sepsis and even death. CVC is a known risk factor for Staphylococcus infection and bacteraemia. Mupirocin is a naturally occurring antibiotic which is active against Staphylococcus aureus including methicillin resistant and beta lactamase producing strains.

A randomized prospective trial was conducted to assess the role of mupirocin ointment as a prophylaxis in catheter related infection in 28 haemodialysis patients. Of these 13 received skin disinfection at CVC insertion site with povidone iodine (control group) and 15 received the same treatment followed by topical application of 2% mupirocin ointment at the cannula site immediately following catheter placement and at the end of each dialysis session. Patients were followed up until catheter removal and were monitored for the development of catheter related infection (CRI).

The proportion of CRI in mupirocin group was significantly lower than control (6.7% vs. 38.4%, $P < 0.05$). Staphylococcus aureus and MRSA bacteraemia was observed in 4 patients (30.7%) in control group and 3 of them died related to sepsis. None of these was observed in the mupirocin group. The hazard ratio of developing catheter related infection was 7.7 times greater in patients not receiving mupirocin.

As a conclusion, topical mupirocin application at the catheter exit site significantly reduced the risk of catheter related infection especially Staphylococcus aureus septicaemia in haemodialysis patients.

INTRODUCTION

Since their introduction in 1980's Central Venous Catheters (CVC) for haemodialysis have come to play an important role in the delivery of dialysis especially in acute renal failure patients or in end stage renal failure patients while awaiting definitive renal replacement therapy.

Unfortunately CVC is a double edge sword. Tremendous advantages that it brings also carry tremendous problems and cost. Among the serious complications include catheter related infection that accounts for a large percentage of nosocomial infection. The emergence of catheter related infection is directly related to the duration of catheterization and the type of catheter used. The longer the catheter is in place, the higher the chances will be for the catheter to be infected and patients with silicon catheter were found to have increased incidence of catheter related infection (1).

There are numerous data with regards to catheter related infection. In a series of 102 catheters studied by Capdevilla in 1993, 40% developed catheter related infection and out of this one third of the catheter had to be removed, another third were removed later after failing antibiotic therapy and only less than a third can be salvaged successfully(2). From Taiwan University Hospital experience, K. Y. Hung et al found that in 135 patients with a total of 168 catheter placement, a total of 21.4% of catheter related infection rate was observed(3).

In another survey of infection associated with central venous catheter by Gosbel IB et al 1995, in Sydney Australia, it was found that in 479 central venous catheter surveyed in 311

patients from April to August 1991, 11% had developed local infection while 6.7% developed systemic infection. Local infection was predictive of systemic infection but its absence did not exclude systemic infection and haemodialysis catheters were responsible for higher systemic infection rate than other catheter types(4).

Patients with chronic or end stage renal failure are also in a state of depressed immune function. Thus infectious complications leading to a high incidence of morbidity and mortality are well documented problems. There is a number of partly interdependent factors responsible for the diminished Polymorphonuclear leukocytes (PMNL) functions (chemotaxis, phagocytosis, intracellular killing by proteolytic enzymes and toxic oxygen radicals) found in uraemia: iron overload, elevated levels of intracellular calcium and haemodialysis treatment per se has been shown to involved in altered PMNL functions. There is also increased clinical evidence for profound defects in the specific immune defense in uraemia, such as the high susceptibility to viral infections in uraemic patients, the deficient responses of their T lymphocytes, and the significantly depressed specific antibody responses (5).

Renal failure patients are already immunocompromised and the insertion of central venous catheter for haemodialysis adds further risk to bacterial infection. The main approach to catheter related infection is prevention, and the current trend in the prevention of catheter related infection is based on the pathogenesis and pathophysiology of the infection.

CRI begins with the simple colonization of a segment of the catheter by bacteria or fungi. These microorganisms grow and multiply, favoured by local factors that interfere with

the patient's immunologic defences for example fibrin sheath adhering to the catheter walls and the structure and make up of the catheter itself. Because the device is in intimate contact with the systemic circulation, it is understandable that catheter infection is often associated with bacteraemia, particularly when the catheter is in use (6).

Microorganisms colonize the catheter by various routes. Migration from the catheter skin interface over the external surface or from the hub over the internal surface of the device to the catheter tip are the most common. Other pathways include haematogenous seeding from a distant focus of bacteraemia (7,8). Approximately about 50% of catheter related infections originate from the skin, 40% from the contaminated hub and 10% from other routes (9,10).

From microbiology of catheter related infection/bacteraemia there is a predominance of skin microorganism such as Staph. epidermidis, Staph. aureus, Bacillus species and Corynbacterium species. This also include the microorganism that contaminate the hands of medical personnel which is responsible for most of the hospital acquired infection such as Pseudomonas aeruginosa, Acinetobacter species, Stenotrophomanas mathophilia, Candida albicans and Candida parapsilosis (11,12,13,14). From Gesbel IE e at 1995, in a prospective survey of infection associated with central venous catheter,it was found that Staphylococci were the predominant isolates and 40% of the methicillin – resistant Staphylococcus aureus bacteraemias detected were due to catheter related infection(5).

Several preventive strategies have been suggested and studied to reduce CRI which included (i) infusion therapy team, (ii) subcutaneous tunneling of CVC, (iii) periodic flushing

of the catheter with an antibiotic solution (intraluminal antibiotic lock), (iv) antimicrobial coating of catheter on the external surface, (v) catheters with new antiseptic hub models and (vi) the use of ionic silver impregnated subcutaneous collagen cuff.

In this study, we applied cutaneous antimicrobial at the catheter exit site with the intention to reduce or lower the microbial burden since this is the most common site of the infection. The topical antibiotic of concern is mupirocin. Mupirocin is a topical broad spectrum antibiotics which is active against staphylococcus aureus, including methicillin-resistant stains, other staphylococci and streptococci. It is also active against gram-negative pathogens such as Escherichia coli and Haemophilus infeluenzae.

METHODOLOGY

1. A prospective randomised controlled study.
2. Patients with acute on chronic renal failure (CRF) or end stage renal failure (ESRF) requiring haemodialysis using CVC as a temporary venous access who satisfied the inclusion criteria and gave written consent were included.

   Inclusion criteria :

   (i) adult patients (age ≥ 13)

   (ii) CVC for haemodialysis inserted into subclavian or internal jugular veins.

   Exclusion criteria :

   (i) pre-existing fever from any focus of infection at study entry

   (ii) patients with acute renal failure

   (iii) CVC over femoral vein
3. Double lumen CVC (Gamcath-Gambro) were inserted by medical officers under aseptic Seldinger technique.
4. Patients were recruited from 4 haemodialysis units in Northeast Malaysia.
5. Patients were randomised into 2 groups. The first group (control) used 10% povidine iodine as skin disinfectant at the catheter insertion site and the second group received the same treatment followed by application of 2% calcium mupirocin ointment.
6. This was carried out after catheter placement and at the end of each dialysis session.
7. Patients in both groups were followed up regularly until their catheters were removed. Inspection of the catheter site was done and body temperature was taken during each dialysis session (3 times each week).
8. All patients had superficial swabs (skin & catheter surface) taken once every week.

9. CRI was classified into 2 categories.

   i. ***Exit Site Infection:*** *infection localised to the catheter exit site characterized by localized redness, crusting & exudates and a positive superficial culture*

   ii. ***Catheter Related Bacteraemia:*** *systemic symptoms (fever, rigors) and positive blood culture.*

10. In patients who developed symptoms and signs suggesting catheter related infection, superficial swabs together with blood cultures were taken from the catheter as well as from peripheral vein.

11. During catheter removal in all patients, superficial swabs and catheter tip were again sent for culture.

12. The endpoints of the study were:-

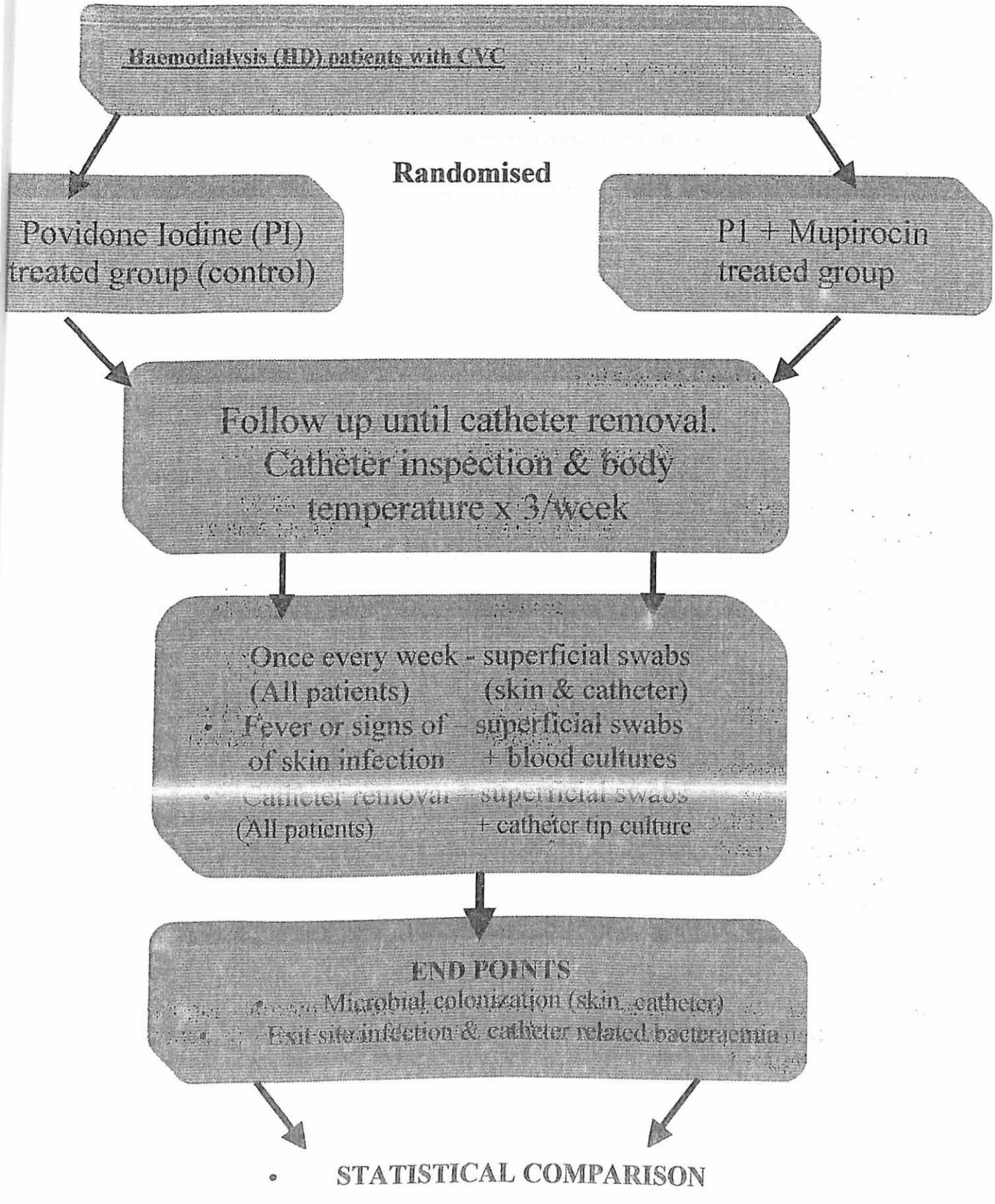
    1.Microbial colonization (skin, catheter)

    2.Catheter related infection

13. The duration of the study was 15 months (between 1st. July 1999 to 30th. September 2000).

14. Statistical analysis was done using SPSS version 9 programme. Student's 't' test was used to compare continuous variables and Fisher's exact test was used to compare proportions.

FLOW CHART OF RESEARCH METHODOLOGY



RESULTS

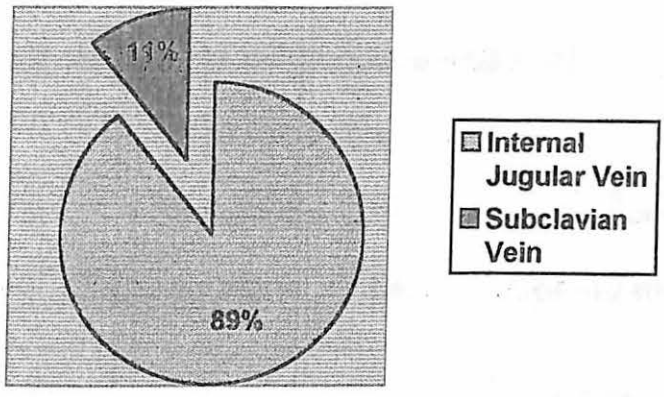
A total of 28 patients were recruited in the study over a -15 month period (from 1st July 1999 to 30th September 2000). Fifteen patients were assigned to prophylaxis with mupirocin and 13 to the control group. The baseline characteristics of the patients in the study are shown in Table 1

Table1. Baseline patient characteristics

Characteristic	Mupirocin (n = 15)	Control (n = 13)
Age, years (mean)	48.13	48.92
Male/Female,n(%)	8/7(53.3/46.7)	7/6(53.8/46.2)
Race,n(%)		
Malay	13(86.6)	11(84.6)
Chinese	2(13.4)	1(7.7)
Indian		
Others		1(7.7)
Diagnosis,n (%)		
Acute on CRF	2(13.4)	2(15.4)
ESRF	13(86.6)	11(84.6)
Comorbid conditions,n		
Hypertension	9	9
Diabetes Mellitus	4	2
Ischaemic heart disease	1	1
Gout	1	1

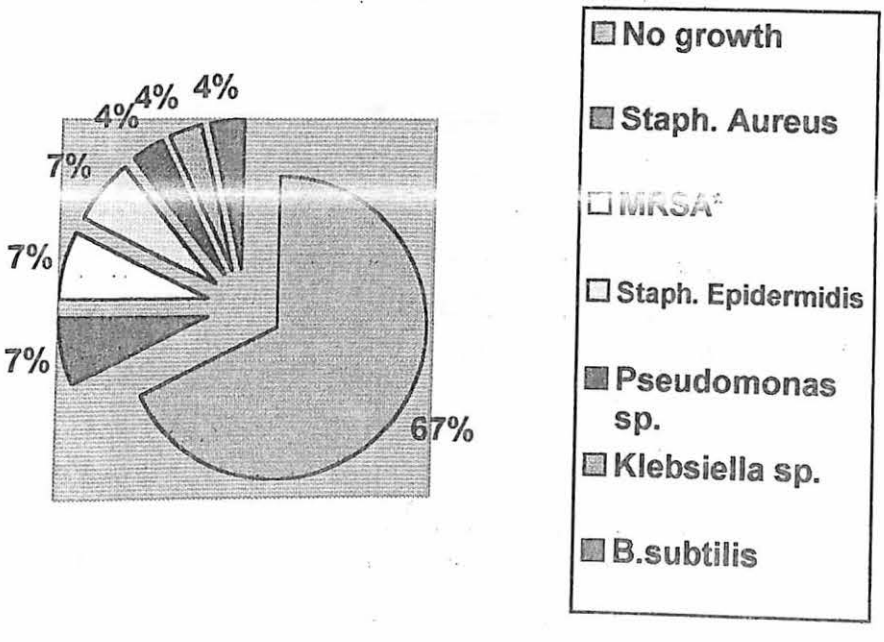
With regards to the site of catheter insertion, internal jugular vein catheterization (25 patients) was preferred to subclavian vein (3 patients), as depicted in Figure 1

Figure 1. Site of catheter insertion



The spectrum of micro-organisms isolated in both treatment groups are illustrated in Figure 2 and tabulated according to colonization or CRI in Table 2. The proportion of patients with CRI in the mupirocin group was much lower than control (6.7% [1 of 15] versus 38.4% [5 of 13], P = 0.045)

Figure 2. Microorganism isolated



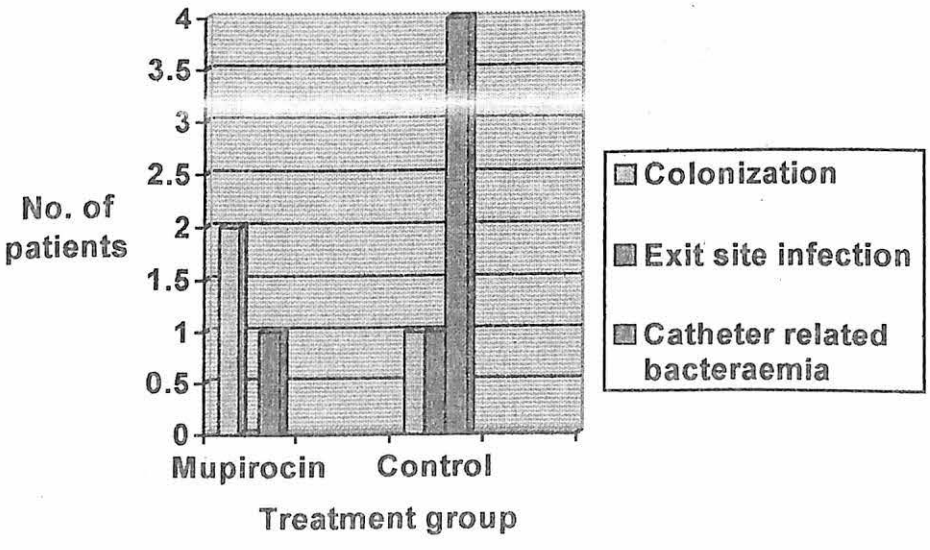
* MRSA = Methicillin resistant Staph. aureus

Table 2. Micro-organism causing colonization and CRI

Microorganism Isolated	Type of dressing			
	Mupirocin (n=15)		Control(n=13)	
	Colonization	CRI	Colonization	CRI
Staph. aureus				2(15.4%)
MRSA				2(15.4)
Staph. epidermidis	1(6.7%)		1(7.6%)	
Pseudomonas sp.				1(7.6%)
Klebsiella sp.		1 (6.7%)		
Bacillus subtilis	1 (6.7%)			
No growth	12 (80.0%)		7(53.8%)	

The microbiological outcome for patients in both groups with regards to bacterial colonization, exit site infection and catheter related bacteraemia are shown in Figure 2

Figure 2. Microbiological outcome



The reasons for catheter removal in both groups are listed in Table 3. Catheter related infection necessitated catheter removal in all the patients in both treatment groups. The mean duration of catheter placement was longer in the mupirocin group compared to control but it was not statistically significant (49.00 days versus 25.15 days, P = 0.053). There were 3 deaths in the control group, all related to CRI but there was no death in the mupirocin group.

Table 3. Reasons for catheter removal

Reasons for catheter removal	Mupirocin (n = 15)	Control (P. Iodine) (n = 13)
Catheter Related Infection	1(6.7%)	5(38.4%)
Available permanent access	11(73.3%)	2(26.0%)
Renal function recovery		2(26.0%)
Catheter blockage	3(20.0%)	2(26.0%)
Catheter slipped out		2(26.0%)

DISCUSSION

In this study cutaneous mupirocin application to the catheter exit site effectively alleviated and reduced the microbial burden especially Staphylococcus aureus and methicillin resistant Staphylococcus aureus which are the main microorganism that cause serious catheter related infection and its complications.

Mupirocin is a naturally occuring antibiotic and is produced by fermentation of the organism Pseudomonas fluorescens. Mupirocin inhibits bacterial protein synthesis by reversibly and specifically binding bacterial isoleucyl transter – RNAsynthetase. Due to this mode of action, mupirocin shows no cross resistance with chloramphenicol, erythromycin, fucidic acid, gentamycin, lincomycin, methicillin, neomycin, novobiocin, penicillin, streptomycin and tetracycline.

Mupirocin is not absorbed into systemic circulation and hence active at epidermal layer. The bacteria that are susceptible to the action of mupirocin are Staphylococcus aureus including methicilin resistant and beta lactamase producing strains, Staphylococcus epidermidis, Staphylococcus saprophyticus and Streptococcus pyogenes.

The outcome of patients with central venous catheter for haemodialysis as shown in figure 3 was observed, there was significant reduction in the number of catheter related infection in mupirocin group (6.7% versus 38.4%, $P = 0.045$). However, in terms of mean duration of catheter placement between the 2 study groups, although patients in the mupirocin group had longer mean duration of catheter placement, ranging from 6 to 154 days, there was

only marginal significance observed (49.00 days versus 25.15, P= 0.053). This could probably be due to the small number of patients who entered the study.

Comparing the microorganisms isolated between the 2 groups, there was significant difference observed. There were only 20% of patients in the mupirocin group who had positive culture compared to 56% patients in the control group, P = 0.012. In the control group, of those who were culture positive, more than 70% had CRI and out of this, 80% is due to Staphylococcus aureus and methicillin resistant Staphylococcus aureus. None of these were observed in mupirocin group.

Previous randomised control trials of mupirocin showed a five to seven fold decrease in the risk of colonization in central venous catheter inserted in jugular vein (15,16). However, this was offset by a higher risk of fungal colonization and infection especially candida species because application of the ointment could interfere with the normal flora of the skin thus favoring fungal growth.. Fortunately none of our patients had fungal isolated especially in the mupirocin group.

Regarding the reasons for catheter removal, referring to table 3, catheter related infection necessitated catheter removal in all the patients in both treatment group (38.4% in the control group vs 6.7% in the povidone group).This carries important implications in terms of the total cost of hospitalization and prolonged antibiotic therapy as well as the extra cost of a new CVC to be inserted later since the CVC is the lifeline for the patients.More than 70% of patients in the mupirocin group had achieved renal replacement therapy either haemodialysis

via AV fistula or through continuous ambulatory peritoneal dialysis compared to only 26% of patients in the control group, $P < 0.05$. This observation reflected better outcome in mupirocin treated group. This finding could be explained by significant reduction in the rate of catheter related infection so the patients had longer duration of catheter placement and more time can be utilized or spent for optimum work up before entering renal replacement programs.

Several preventive strategies against catheter related infection have been studied and practiced including subcutaneous tunelling, intraluminal antibiotic locks and antiseptic hubs. These methods requires technical expertise and good financial status to maintain their use. The more economical and simple measure as in this study was by applying cutaneous antimicrobial at the catheter exit site with the intention to reduce or lower the microbial burden since this is the commonest site of entry of microorganism.

Although it has not gained much attention in the prevention of CRI, mupirocin is a very useful drug due to its unique pharmacokinetics and most importantly it does not show cross resistance with most antibiotics. We also found that mupirocin is safe to be used since there were no adverse events observed during the trial phase.

CONCLUSION

This study has shown that topical application of mupirocin ointment at the catheter exit site effectively reduced catheter-related infection in chronic renal failure patients on haemodialysis using CVC. Mupirocin is also safe and easy to be used as well as more economical when compared to most of other preventive methods against CRI.

ACKNOWLEDGEMENT

My gratitude goes to the following people who have been directly involved in this research project: (i) Dr. Azeril Haris Yafee Amar, Masters of Medicine candidate (ii) Dr. Mohd Zaki Salleh, Consultant Microbiologist in Department of Microbiology, School of Medical Science, U.S.M (iii) Puan Maimunah, Microbiology Laboratory Technician and (iv) Puan Rohani Sulaiman, our research assistant.

I greatly appreciate the cooperation given by all haemodialysis staff and the patients involved from Hospital Universiti Sains Malaysia, Hospital Kota Bharu, Hospital Kuala Terengganu and Renal Care Dialysis Centre.

I would like to acknowledge the Office of the Deputy Director – General of Health Malaysia (Research & Technical Support) for granting permission to include patients from Ministry of Health hospitals. Finally I would like to express my gratitude to Universiti Sains Malaysia that has provided IRPA Short Term Research Grant (No: 305.PPSP.6121045) which has supported this study.

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