Original Article

Prophylactic use of Mupirocin in hemodialysis central venous catheters: a systematic review and meta-analysis

Uso profilático de Mupirocina em cateter venoso central de hemodiálise: revisão sistemática e metanálise

Uso profiláctico de Mupirocina en cateter venoso central de hemodiálisis: revisión sistemática y metaanálisis

Mônica Taminato[1], Dayana Souza Fram[1], Cibele Grothe[2], Angélica Gonçalves Silva Belasco[3], Dulce Aparecida Barbosa[4]

ABSTRACT

Objective: To evaluate the impact of the use of topical Mupirocin on the insertion of central venous catheter for hemodialysis. **Methods:** This was a systematic review with meta-analysis. **Results:** After a careful and extensive search, we included three clinical trials that compared the use of Mupirocin versus other intervention in central venous catheter for hemodialysis. **Conclusion:** The study found that the use of topical Mupirocin is effective in reducing episodes of infection among hemodialysis patients, increasing duration time for catheter, and significantly reducing *S aureus* infections, which are the most prevalent in this population.

Keywords: Renal dialysis; Catheterization central venous; Mupirocina; *S aureus;* Meta-Analysis

RESUMO

Objetivo: Avaliar o impacto do uso de Mupirocina tópica em inserção de cateter venoso central para hemodiálise. **Métodos:** Revisão Sistemática com Metanálise. **Resultados:** Após uma criteriosa e extensa busca, foram incluídos três ensaios clínicos que compararam o uso de Mupirocina *versus* outra intervenção em cateter venoso central para hemodiálise. **Conclusão:** O estudo apontou que o uso de Mupirocina tópica é eficaz para redução dos episódios de infecções entre os pacientes em hemodiálise, aumentando o tempo de utilização do cateter, além de reduzir significativamente as infecções por *S aureus* as mais prevalentes nessa população.

Descritores: Hemodiálise; Cateterismo venoso central*;* Mupirocina*; S aureus*; Metanálise

RESUMEN

Objetivo: Evaluar el impacto del uso de Mupirocina tópica en inserción de cateter venoso central para hemodiálisis. **Métodos:** Revisión Sistemática con Metaanálisis. **Resultados:** Después de una criteriosa y extensa búsqueda, se incluyeron tres ensayos clínicos que compararon el uso de Mupirocina versus otra intervención en cateter venoso central para hemodiálise. **Conclusión:** El estudio demostró que el uso de Mupirocina tópica es eficaz para la reducción de los episodios de infecciones entre los pacientes en hemodiálisis, aumentando el tiempo de utilización del cateter, además de reducir significativamente las infecciones por *S aureus*, las más prevalentes en esa población.

Descriptores: Diálisis renal; Cateterismo venoso central; Mupirocina*; S aureus;* Metanálisis

[1] *Master's of Science, Paulista School of Nursing, Federal University of São Paulo (UNIFESP) - São Paulo (SP), Brasil.*
[2] *Doctorate in Sciences, Paulista School of Nursing, Federal University of São Paulo (UNIFESP) - São Paulo (SP), Brasil*
[3] *Post-doctorate in Sciences. Adjunct Professor, Paulista School of Nursing, Federal University of São Paulo (UNIFESP) - São Paulo (SP), Brasil*
[4] *"Livre Docente." Associate Professor, Paulista School of Nursing, Federal University of São Paulo (UNIFESP) - São Paulo (SP), Brasil*

Corresponding Author: **Dulce Aparecida Barbosa**
Rua Napoleão de Barros, 754
Vila Clementino – São Paulo – SP – Brasil
e-mail: dulce.barbosa@unifesp.br

Received article **05/06/2011** and accepted **07/08/2011**

INTRODUCTION

In hemodialysis, central venous catheters (CVC) provide a rapid and temporary access alternative for the establishment of treatment in patients with acute or terminal kidney disease. The use of CVCs should be quite limited due to the frequent occurrence of bloodstream infection; as shown in several studies, the rate is approximately 40% [1–7].

Infection is the second leading cause of mortality among patients with end stage renal disease (ESRD) and represents, approximately, 14% of deaths among these individuals, preceded only by cardiovascular events [8].

According to the National Census of the Brazilian Society of Nephrology, the number of patients on dialysis treatment in Brazil, in 2007, was 73,605; and, of these, 90.8%, received hemodialysis [9].

Patients receiving hemodialysis have a high risk of infection due to the immunosuppressive effects caused by ESRD, comorbidities, inadequate nutrition and the need for maintenance of vascular access for long periods. In dialysis centers, many patients are undergoing hemodialysis simultaneously, which facilitates the spread of microorganisms by direct or indirect contact through the devices, equipment, surface contact, and hands of health professionals [4,10]. However, the quality of dialysis and, consequently, the well-being and survival of the patient depend on vascular access; on the other hand, it is considered the major risk factor for infection, and particularly, of bacteremia in this patient population [11].

Central venous access is considered a less suitable alternative in relation to arteriovenous fistula, as recommended by K/DOQI (*Kidney Disease Outcome Quality Initiative*) [12]. Despite the recommendations of the *Dialysis Outcomes and Practice Patterns Study* (DOPPS II), studies show that the use of CVC for hemodialysis among patients in Europe and Canada varies between 46% to 70% of these patients. The high use of CVC for hemodialysis may reflect: a delayed search for a nephrologist, initiation of therapy in emergency situations, patients with diabetes and major vascular compromise, and lack of experience on the part of professionals in inserting a fistula [13-15].

A study conducted at the Federal University of São Paulo showed a bacteremia incidence of 61% among patients with ESRD when using CVC. Risk factors for developing bacteremia were: implantation of a catheter into the subclavian vein, length of time catheter was in place, and length of hospitalization. The mortality rate in these patients was 29%, and for those who progressed to endocarditis, the mortality rate was 55.5%[16].

The rate of infection related to CVC for hemodialysis was significantly reduced with regular use of topical Mupirocin at the insertion site. The data were positive for catheters with or without cuff and for those that were tunneled and not tunneled [1,17]. Mupirocin is an antibiotic that is active against gram positive organisms [18].

Motivated by the importance of infections associated with the use of CVC for hemodialysis, and their impact on the number of hospitalizations, catheter changes, bacteremia and death related to infection, this systematic review with meta-analysis was conducted with support of the Paulista School of Nursing / UNIFESP and the Cochrane Collaboration in Brazil. The principal objectives of this review were to evaluate the impact of the use of topical Mupirocin at the insertion site of CVC in hemodialysis, and the occurrence of infectious events related to the use of CVC for hemodialysis, bacteremia and bacteremia caused by *Staphylococcus aureus*.

METHODS

This systematic review with meta-analysis followed the steps proposed by the Cochrane Collaboration [19] and used the PICO strategy, which is an acronym for: **P**atient, **I**ntervention, **C**omparison and **O**utcomes [20]. Studies were included regardless of language or form of publication, such as those that compared the use of topical Mupirocin versus other interventions in the insertion of CVC for hemodialysis.

Exclusion criteria were those articles that did not evaluate outcomes relevant to this research.

Strategies for identifying the studies

The relevant studies were identified using electronic database searches of: the *Cochrane Library* (including "*The Cochrane Controlled Trials Register"* contained in the *"Cochrane Library"* 2010, volume 10); PUBMED (January 1966 to January 2010); EMBASE (January 1985 to December 2010); LILACS (January 1982 to December 2010); SciELO (June 1998 to December 2010); CINAHL(June 1981 to December 2010); the database available at: www.controlledtrials.com; abstracts of papers presented at conferences; review articles; systematic reviews; and, randomized clinical trials were identified. The main keywords in the search strategy were: ("mupirocin"[MeSH Terms] OR "mupirocin"[All Fields]) AND ("haemodialysis"[All Fields] OR "renal dialysis"[MeSH Terms] OR ("renal"[All Fields] AND "dialysis"[All Fields]) OR "renal dialysis"[All Fields] OR "hemodialysis"[All Fields]).

Selection of the studies

The articles were read by two independent reviewers (A and B) in order to ascertain whether they fulfilled

the inclusion criteria. Reviewers were not blinded; they assessed the titles and abstracts of identified studies and obtained complete photocopies of relevant articles. In case of doubt or disagreement, a third reviewer (C) was asked to express an opinion as to whether the study should or should not be included in the research.

Evaluation of methodological quality and statistical analysis

Methodological quality was defined as the confidence that the study and its presentation within the article would be free of bias [19]. Thus, articles were first stratified according to the type of design and, subsequently, in relation to the outcome, following the Cochrane methodology [19].

The *Review Manager 5* [21], provided by *The Cochrane Collaboration*, was utilized for statistical analysis. For dichotomous variables, the *odds ratio* (OR) with a confidence interval of 95% was calculated using random and fixed models. For calculation of heterogeneity, we used the Mantel-Haenszel chi-square and I^2 index [19].

RESULTS

After an extensive bibliographic search, we identified 161 studies from the following databases: 147 PUBMED, 7 EMBASE, 1 LILACS, and 6 through manual review of references within the studies. During the pre-selection, 25 studies were identified by one reviewer and 22 by another reviewer. The discrepancies were resolved by a third reviewer. Finally, three studies were included in this review: Sesso et al. [1], Johnson et al. [17], and Johnson et al. [22]

All of the studies were evaluated and classified as low risk of bias and having adequate methodological quality by the Cochrane reference [19]. Randomization of the three studies included in this review was completed by computer, allocation concealment was adequate and the analysis was based on intention to treat.

The studies of Sesso et al., [1] and Jonhson et al. [17] (182 participants) included in the review compared the use of mupirocin topically for catheter insertion versus those without intervention, namely, wound dressing with the standard alcoholic solution of PVPI. And another study by Johnson et al. [22], compared the use of topical Mupirocin versus honey (101 participants).

As shown in Figure 1, infectious complications related to central venous catheters were significantly reduced in patients using topical Mupirocin in catheter insertion as compared with patients without intervention, (RR 0.15, 95% CI 0.05 - 0.46). There was no significant heterogeneity between studies ($Chi^2 = 0.30$, $I2 = 0\%$, $P = 0.59$).

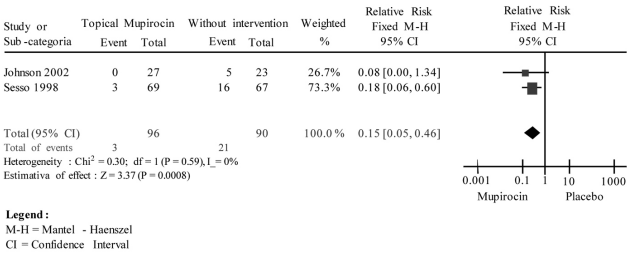

Figure 1. Infectious complications related to the use of central venous catheters for hemodialysis comparing topical Mupirocin *versus* no intervention

Figure 2 shows that the occurrence of bacteremia related to central venous catheters was significantly reduced in patients who used topical Mupirocin on catheter insertion compared to the patient group without the intervention, RR 0,11, 95% IC 0.04 -0.35. There was no significant heterogeneity between studies ($Chi^2 = 0.15$, $I^2 = 0\%$, p=0.69).

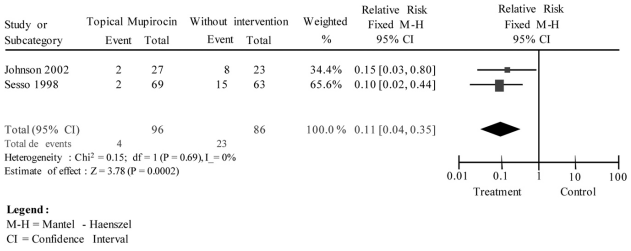

Figure 2. Bacteremia when comparing topical Mupirocin *versus* no intervention

Figure 3 shows that there was a significant reduction in bacteremia caused by *S. aureus* in the intervention group compared to the control group, RR 0,07 [0.01-0.40]. There was no significant heterogeneity between studies ($Chi^2 = 0.00$, $I^2 = 0\%$, P=0.95).

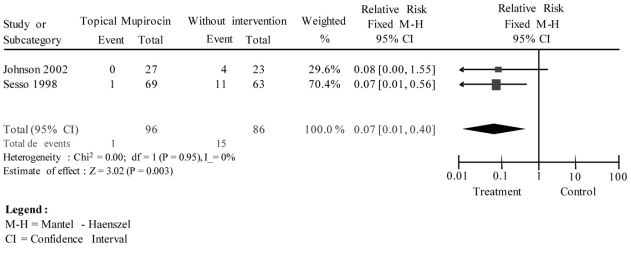

Figure 3. Bacteremia caused by *S. aureus* when comparing topical Mupirocin *versus* no intervention

In Figure 4, the results are shown for interventions of topical Mupirocin *versus* honey in catheter insertion, from a single study that assessed the occurrence of bacteremia caused by *S. aureus* related to the use of CVC. The data were not significant, (RR 1.02, 95% CI 0.06 -16.77).

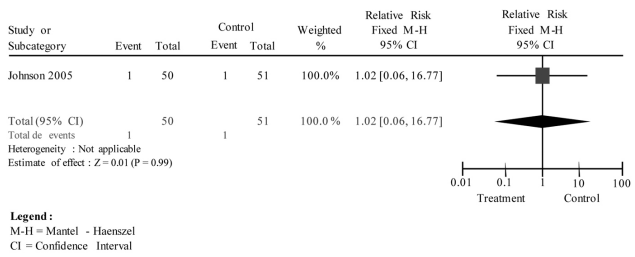

Figure 4 – Bacteremia caused by *S. Aureus*, comparing topical Mupirocin *versus* honey

DISCUSSION

The principal objective of this study was to evaluate the impact of the use of topical Mupirocin in the insertion of CVC used for hemodialysis, and the results point to a significant reduction in the occurrences of infectious events, bacteremias and bacteremias caused by *S. Aureus*.

The methodology of this systematic review was rigorous, following the Cochrane recommendations: the whole process was performed by two independent reviewers, the search strategy was broad, and, there was no language restriction. Thus, each included study was assessed for methodological quality and for heterogeneity among the studies. All these steps were intended to reduce the possibility of biases, in order to provide greater credibility of the results.

After a careful search for articles in several databases, abstracts of papers presented at conferences, and the references of published review and systematic review articles, we identified 174 relevant articles. Of these, only three met the criteria for inclusion in the study, which was that the articles must be about the use of Mupirocin versus control (placebo or honey) in CVC for hemodialysis.

Sesso et al., [1] and Johnson et al. [17] reported similar results of studies that evaluated the use of Mupirocin *versus* no intervention, and about the protective effect of Mupirocin in regard to infectious complications, bacteremia and bacteremia caused by *S. aureus* related to the use of CVC.

Among those works, there were differences in the type of catheter used for hemodialysis: nontunneled and without *cuff* for patients followed by Sesso et al.; [1] tunneled and with *cuff* in those followed by Johnson et. al [17]. Many randomized clinical trials and reviews have clearly demonstrated that the use of tunneled catheters and those with cuffs reduce the risks of catheter-related sepsis by 44% -77% as compared to the use of non-tunneled catheters and those without cuff, by reducing the risks of bacterial migration from the skin to the circulation and diminishing the formation of biofilm [6,8,13,23].

There was no statistically significant difference in regard to the use of Mupirocin *versus* honey for bacteremias caused by *S. aureus*. Historically, honey was used for its antibacterial action, especially in wounds. But randomized clinical trials that have evaluated its effects are recent, with promising results for a therapeutic alternative for preventing bacterial resistance and causing few adverse events [24-25] .

This systematic review with metaanalysis provides evidence of the beneficial effect of the use of Mupirocin with insertion of CVC for hemodialysis, for the preventative action against infectious complications and bacteremias for all causes including *S. aureus*. This systematic review and meta-analysis showed the beneficial effect of the use of Mupirocin for the insertion of CVC for hemodialysis, and for prevention of infectious complications and bacteremia, particularly those caused by *S. aureus*. One study showed that the topical use of Mupirocin at the catheter site for hemodialysis reduced the development of *S. aureus*-related infections by 80% [26].

Some research also demonstrated the cost-benefit advantages related to the use of Mupirocin at the catheter insertion site for hemodialysis, for significantly reducing the rates of infection related to the catheters, also diminishing the costs of medical and hospital-related procedures [26-27].

CONCLUSION

In terms of a conclusion for this study and implications for clinical practice, the use of topical Mupirocin is effective in reducing episodes of infections and, especially, bacteremias related to CVC in this patient population; it also allows longer use of CVC without infection. Another striking factor was the significant reduction of infections caused by *S. aureus*, the most prevalent among these patients. New randomized clinical trials should be conducted to address this issue, given the scarcity of studies in the area.

REFERENCES

1. Sesso R, Barbosa D, Leme Il, Sader H, Canziani ME, Manfredi S, et al. Staphylococcus aureus prophylaxis in hemodialysis patients using central venous catheter: effect of mupirocin ointment. J Am Soc Nephrol 1998; 9(6):1085–92.
2. Randolph AG, Cook DJ, Gonzales CA, Brun-Buisson C. Tunneling short-term central venous catheters to prevent catheter-related infection: a meta-analysis of randomized,controlled trials. Crit Care Med. 1998; 26(8): 1452–7.
3. Swartz RD, Messana JM, Boyer CJ, Lunde NM, Weitzel WF, Hartman TL, et al. Successful use of cuffed central venous hemodialysis catheters inserted percutaneously. J Am Soc Nephrol. 1994; 4(9):1719–25.
4. Boelaert JR, Van Landuyt HW, Godard CA, Daneels RF, Schurgers ML, Matthys EG, et al. Nasal mupirocin ointment decreases the

incidence of Staphylococcus aureus bacteraemias in haemodialysis patients. Nephrol Dial Transplant 1993; 8(3): 235–9.
5. Moss AH, Vasilakis C, Holley JL, Foulks CJ, Pillai K, McDowell DE. Use of a silicone dual-lumen catheter with a Dacron cuff as a long-term vascular access for hemodialysis patients. Am J Kidney Dis. 1990;16(3):211–5.
6. Flowers RH 3rd, Schwenzer KJ, Kopel RF, Fisch MJ, Tucker SI, Farr BM. Efficacy of an attachable subcutaneous cuff for the prevention of intravascular catheter-related infection. A randomized, controlled trial. JAMA. 1989; 261(6): 878–83.
7. Schwab SJ, Buller GL, McCann RL, Bollinger RR, Stickel DL. Prospective evaluation of a Dacron cuffed hemodialysis catheter for prolonged use. Am J Kidney Dis. 1988; 11(2):166–9.
8. Center for Disease Control and Prevention: Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR. 2001; 50(RR- 5)
9. Sociedade Brasileira de Nefrologia. Censo nacional 2007. São Paulo (SP):SBN; 2007.
10. Fram DS, Taminato M, Ferreira D, Neves L, Belasco AG, Barbosa DA. Prevention of catheter-related bloodstream infections in patients on hemodialysis. Acta Paul Enferm. 2009; 22(N Espec): 564-8.
11. Mangini C, Camargo LF, coordenadores. Prevenção de infecção relacionada à diálise. São Paulo: Associação Paulista de Estudos e Controle de Infecção Hospitalar; 2005.
12. Vascular Access Work Group. Clinical practice guideline for vascular access. Am J Kidney Dis. 2006. 48 Suppl 1: S248-73.
13. Mendelssohn DC, Ethier J, Elder SJ, Saran R, Port FK, Pisoni RL. Haemodialysis vascular access problems in Canada: results from the dialysis outcomes and practice patterns study (DOPPS II). Nephrol Dial Transplant. 2006;21(3):721-8.
14. Létourneau I, Ouimet D, Dumont M, Pichette V, Leblanc M. Renal replacement in end-stage renal disease patients over 75 years old. Am J Nephrol. 2003;23(2):71-7.
15. Butterly DW, Schwab SJ. Catheter access for hemodialysis: an overview. Semin Dial. 2001;14(6):411-5.
16. Grothe C, Belasco A, Bettencourt A, Diccini S, Vianna L, Sesso R, Barbosa D. High incidence of bacteremia among patients undergoing hemodialysis. Rev Latinoam Enferm. Forthcoming 2009.
17. Johnson DW, MacGinley R, Kay TD, Hawley CM, Campbell SB, Isbel NM. A randomized controlled trial of topical exit site mupirocin application in patients with tunnelled, cuffed haemodialysis catheters. Nephrol Dial Transplant. 2002;17(10):1802-7.
18. van Rijen M, Bonten M, Wenzel R, Kluytmans J. Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Cochrane Database of Syst Rev. 2008 (4):CD006216.
19. Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of intervention. Chichester (UK): John Wiley & Sons; 2005.
20. Santos CM, Pimenta CA, Nobre MR. The PICO strategy for the research question construction and evidence search. Rev Latinoam Enferm. 2007; 15(3):508-11.
21. RevMan Analyses Version 1.0 for Windows, in Review Manager 5.1 Oxford England : The Cochrane Collaboration; 2005.
22. Johnson DW, van Eps C, Mudge DW, Wiggins KJ, Armstrong K, Hawley CM, et al. Randomized, controlled trial of topical exit-site application of honey (Medihoney) versus mupirocin for the prevention of catheter-associated infections in hemodialysis patients. J Am Soc Nephrol. 2005;16(5):1456-62.
23. Randolph AG, Cook DJ, Gonzales CA, Brun-Buisson C. Tunneling short-term central venous catheters to prevent catheter-related infections: a meta-analysis of randomized, controlled trials. Crit Care Med. 1998;26(8):1452-7.
24. Jull A, Walker N, Paraq V, Molan P, Rodgers A; Honey as Adjuvant Leg Ulcer Therapy trial collaborators. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. Br J Surg. 2008;95(2):175-82.
25. French VM, Cooper RA, Molan PC. The antibacterial activity of honey against coagulase-negative staphylococci. J Antimicrob Chemother. 2005;56 (1):228-231.
26. Tacconelli E, Carmeli Y, Aizer A, Ferreira G, Foreman MG, D'Agata EM. Mupirocin prophylaxis to prevent Staphylococcus aureus infection in patients undergoing dialysis: a meta-analysis. Clin Infect Dis. 2003;37(12):1629-38.
27. Bloom BS, Fendrick AM, Chernew ME, Patel P. Clinical and economic effects of mupirocin calcium on preventing Staphylococcus aureus infection in hemodialysis patients: a decision analysis. Am J Kidney Dis. 1996;27(5):687-94.