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The Role of Antimicrobial-Impregnated Catheters on Catheter-Related Bloodstream Infection Prevention

Leonardo Lorente[1,*]

[1]Intensive Care Unit, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

*Corresponding author: Leonardo Lorente, Intensive Care Unit, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain. Tel: +34-922678000, Fax: +34-922647112, E-mail: lorentemartin@msn.com.

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Abstract

Context: The catheterization of a central venous catheter (CVC) may be needed due to different motives. However, that central venous catheterization has different risks such as infection, which leads to morbidity, mortality and assistant costs. Different measures to prevent catheter-related infection have been proposed.

Evidence Acquisition: Electronic medical data bases (including PubMed and Scopus) from first of January 1975 to 30th of July 2015 were searched. The key words used for the relevant articles search were catheter, venous, prevention, impregnated, bloodstream, chlorhexidine-silver sulfadiazine, rifampicin-minocycline, and rifampicin-miconazole. This review focuses on the evidence on the efficacy and efficiency of antimicrobial impregnated catheters for the prevention of catheter-related bloodstream infections (CRBSI).

Results: The use of catheters impregnated in different antimicrobial agents has been found to be an effective and efficient measure for the prevention of CRBSI. Most antimicrobial agents used for such impregnation have been chlorhexidine silver sulfadiazine (CHSS), rifampicin-minocycline, and rifampicin-miconazole. The use of a CHSS or rifampicin-minocycline impregnated catheter in patients has been recommended by the current guidelines for the prevention of CRBSI when CVC is expected to remain in place for > 5 days and if the CRBSI rate has not decreased after implementation of a comprehensive strategy.

Conclusions: Based on the current knowledge, it can be assumed that the use of antimicrobial impregnated catheters could be considered in some clinical circumstances associated with higher risk of CRBSI, such as patients with a CVC in the internal jugular venous site with the presence of tracheostomy or in the femoral venous site.

Keywords: Bloodstream, Catheter, Impregnated, Prevention, Venous

1. Context

The catheterization of a central venous catheter (CVC) may be needed due to different reasons, such as the administration of blood products, parenteral nutrition, fluids, medications, or for the monitoring of hemodynamic status. However, central venous catheterization has different risks such as haemorrhage, thrombosis and infection. The concern about catheter-related infection lies in the morbidity, mortality and assistant costs that are involved (1-9). Different measures to prevent catheter-related infection have been proposed (10).

2. Evidence Acquisition

Electronic medical databases (including PubMed and Scopus) from 1st of January 1975 to 30th of July 2015 were searched. The key words used in the search for relevant articles were catheter, venous, prevention, impregnated, bloodstream, chlorhexidine-silver sulfadiazine, rifampicin-minocycline and rifampicin-miconazole. This review focuses on the evidence about the efficacy and efficiency of antimicrobial impregnated catheters for the prevention of catheter-related bloodstream infections (CRBSI).

3. Results

3.1. Evidence About the Efficacy of Antimicrobial Impregnated Catheters to Reduce the Incidence of CRBSI

The use of CVC impregnated with different antimicrobial agents, such as chlorhexidine-silver sulfadiazine (CHSS), rifampicin-minocycline, rifampicin-miconazole, cefazolin, vancomycin, heparin, platinum and carbon has been proposed for the prevention of CRBSI (11).

In a meta-analysis by Veenstra et al., including 11 randomized clinical trials (RCT) and 2603 catheters, it was found that the use of first-generation CHSS impregnated catheters (impregnated only on the external surface) reduced the risk of CRBSI compared with non-impregnated

catheters (odds ratio (OR) = 0.56; 95% confidence interval (CI) = 0.37-0.84; P = 0.005) (12). Later, second-generation CHSS impregnated catheters were developed (impregnated on both, the external and internal surfaces), and in a meta-analysis (13), including three RCTs and 1176 patients (14-16), it was found that these catheters reduced the risk of CRBSI compared to standard catheters.

Another meta-analysis by Falagas et al., including 3452 CVCs from eight RCTs revealed a reduction of CRBSI with the use of antimicrobial impregnated catheters compared with non-coated catheters (17). In this meta-analysis seven RCTs using rifampicin-minocycline impregnated catheters and one RCT using a rifampicin-miconazole impregnated catheter were included.

In one study by our team, it was found that the use of rifampicin-miconazole (RM) impregnated catheters decreased the risk of CRBSI (18). We included 241 CVC at a jugular site by central access (114 RM and 127 standard catheters) and 184 CVC at a femoral site (73 RM and 111 standard catheters). This study found that patients with RM impregnated catheters had a lower incidence of CRBSI in jugular venous access (0 vs 4.93 events of CRBSI per 1000 days of catheter, OR = 0.13, 95% CI = 0.00-0.93; P = 0.04) and in femoral venous access (0 vs 8.62 events of CRBSI per 1000 days of catheter, OR = 0.13, 95% CI = 0.00-0.86; P = 0.03) compared with those with standard catheters.

3.2. Evidence Regarding the Efficiency of Rifampicin-Miconazole Impregnated Catheters

After it was found that RM impregnated catheters showed a lower risk of CRBSI than standard catheters, it was interesting to analyze whether RM impregnated catheters could save assistance costs. Thus, we carried out some cost-effectiveness analyses with the use of RM impregnated catheters in the jugular venous access with tracheostomy and in the femoral venous access (19, 20). In one study, including 68 RM and 79 standard catheters in the jugular venous access with tracheostomy, it was found that patients with RM impregnated catheters showed a lower incidence of CRBSI (0 vs 20.16 CRBSI episodes/1000 days of catheter; OR = 0.05; 95% CI = 0.001-0.32; P < 0.001) and a lower immediate catheter related cost per day (€ 11.46 ± 6.25 vs 38.11 ± 77.25; P < 0.001) compared to standard catheters (19). In one study, including 184 RM and 190 standard catheters in the femoral venous access, it was found that patients with standard catheters showed a higher incidence of CRBSI (8.61 vs. 0 CRBSI episodes per 1000 days of catheter; OR = 19.26; 95% CI = 3.24-infinite; P < 0.001) and a higher immediate catheter related cost per day (€ 18.22 ± 53.13 vs. 12.61 ± 8.38; p < 0.001) than patients with RM catheters (20). We studied the efficiency of RM impregnated catheters in those with vascular access (jugular venous access with tracheostomy and femoral venous access) as these patients are at a higher risk of CRBSI.

In another study carried out by our tem, including 2595 CVC (1390 with internal jugular, 917 with subclavian, and 288 with femoral venous access), there was a higher CRBSI incidence in femoral when compared to subclavian accesses (8.34 vs 0.97 events of CRBSI per 1000 days of catheter, P < 0.001), in femoral than in jugular (8.34 vs 2.99 events of CRBSI per 1000 days of catheter, P = 0.002) and in jugular than in subclavian access (2.99 vs 0.97 events of CRBSI per 1000 days of catheter, P = 0.005) (21). Later, in a systematic review by Marik et al., it was concluded that there is no significant difference in the risk of CRBSI between the femoral and internal jugular venous sites, and between the femoral and subclavian venous sites, including two RCTs and eight observational studies (22). It is important to note that the authors excluded two studies from the analysis (the study by our team (21), and a study by Nagashima et al. (23)) to establish such conclusions. However, the decision to exclude these two studies from the analysis was not argued well (24). The two studies were not included in the analysis based on heterogeneity; however, in the methods section the authors stated that $I2 \geq 49\%$ and $P \leq 0.10$ indicated significant heterogeneity, and the heterogeneity analysis showed I2 = 35% and P = 0.14 in the two excluded studies. Furthermore, femoral venous access showed a higher risk of CRBSI than internal jugular site (RR = 1.90; 95% CI = 1.21-2.97; P = 0.005) when those two studies were included in the analysis. The guidelines for the prevention of intravascular catheter-related infections recommend the avoidance of the femoral vein, and the use of the subclavian site rather than jugular or femoral sites to minimize the risk of infection for non-tunnelled CVC placement (10).

Another issue about the incidence of CRBSI is the influence of different accesses on the cannulation of internal jugular venous. In a study by our team, including 515 internal jugular venous catheters by central access and 169 by posterior access, it was found that jugular venous catheters by central access showed a higher incidence of CRBSI than in the posterior access group (4.8 vs 1.2 events of CRBSI per 1000 days of catheter; OR = 3.9; 95% CI = 1.1-infinite; P = 0.03) (25). These findings could probably be due to lower risk of catheter contamination by oropharyngeal secretion in the posterior access. Guidelines for the prevention of ventilator associated pneumonia of the society for healthcare epidemiology of america/infectious diseases society of america (SHEA/IDSA) recommended that critically ill patients undergoing mechanical ventilation should be placed in a semirecumbent position (elevating the head of the bed) to decrease the risk of oesophageal reflux and subsequent aspiration (26). Thus, oropharyngeal secretions could reach the central internal jugular venous access more easily when compared to posterior access in that position due to gravity. In a later study, we found a higher incidence of CRBSI in femoral than in central internal jugular venous access (9.52 vs 4.83 events of CRBSI/1000 catheter days; RR = 1.93; 95% CI = 1.03-3.73; P = 0.04) including 208 femoral catheters and 515 central internal jugular venous catheters (27). Besides, in another study including 877 subclavian and 169 posterior internal jugular venous accesses, we did not find differences in the incidence of

CRBSI between the two accesses (1.02 vs 1.21 events of CRBSI per 1000 days of catheter; P = 0.99) (28). However, there is no recommendation about the use of different jugular venous access sites in the guidelines for the prevention of intravascular catheter-related infections (10).

Other factors such as the presence of tracheostomy have been associated with higher risk of CRBSI (29, 30). In a study by Garnacho-Montero et al., which included 1211 subclavian or jugular venous catheters, it was found that the presence of tracheostomy was associated with a higher risk of CRBSI; however, there has been no report that compares the risk of CRBSI between the two venous accesses (subclavian or jugular) with the presence of tracheostomy (29). In another study by our team, including 515 central internal jugular venous catheters (52 with tracheostomy and 463 without tracheostomy) and 877 subclavian venous catheters (89 with tracheostomy and 788 without tracheostomy), a higher incidence of CRBSI in patients with tracheostomy was found when compared to those without tracheostomy (11.25 vs 1.43 events of CRBSI per 1000 days of catheter; OR = 7.99; 95% CI = 4.38-infinite; P < 0.001). Besides, it was found that patients with the presence of tracheostomy in the jugular venous access showed a higher incidence of CRBSI than those patients with the presence of tracheostomy in the subclavian venous site (21.64 vs 5.11 events of CRBSI per 1000 days of catheter; OR = 4.23; 95% CI = 1.44-infinite; P = 0.01) (30). Furthermore, we found that patients with central internal jugular catheters and tracheostomy had a higher incidence of CRBSI that those with femoral catheters (21.64 vs 9.52 events of CRBSI per 1000 days of catheter; RR = 2.27; 95% CI = 1.04-4.97; P = 0.04) (31), in a study including 52 central internal jugular catheters with tracheostomy and 208 femoral catheters. In another analysis by our team, it was found that patients with subclavian venous access in the presence of tracheostomy showed a lower incidence of CRBSI than patients with femoral venous catheters (3.9 vs 10.1 events of CRBSI per 1000 days of catheter; OR = 0.39; 95% CI = 0.001 – 0.910; P = 0.03) including 147 subclavian venous catheters in the presence of tracheostomy and 313 femoral venous catheters (32). In addition, we found that patients with a posterior jugular venous access in the presence of tracheostomy showed a higher incidence of CRBSI than those without tracheostomy (13.24 vs 0 events of CRBSI per 1000 days of catheter; OR = 23.92; 95% CI = 1.86-infinite; P = 0.008) including 169 CVCs by the posterior jugular venous access (153 without tracheostomy and 16 CVCs with tracheostomy) (33). However, there are no recommendations about the presence of tracheostomy in the guidelines for the prevention of intravascular catheter-related infections (10).

3.3. Evidence About the Efficiency of Chlorhexidine-Silver Sulfadiazine Impregnated Catheters

Later, we found that RM impregnated catheters were an efficient measure for the prevention of CRBSI, and it became interesting to analyze whether CHSS impregnated catheters could also save assistance costs. Thus, we studied the cost-effectiveness of the use of second generation CHSS impregnated catheters in different venous accesses (34-36). We found that patients with CHSS in femoral venous access showed a lower CRBSI incidence (8.61 vs 0.0 CRBSI per 1000 days of catheter; Odds Ratio = 0.12; 95% CI = 0.001-0.72; P = 0.009), and lower CVC-related cost per day of catheter (€ 18.22 ± 53.13 vs 2.92 ± 1.77; P < 0.001) than patients with standard catheters, including 190 standard catheters during 1626 days and 64 CHSS during 569 days (34). In addition, we found that patients with CHSS in jugular venous access showed a lower incidence of CRBSI (0 vs 5.04 CRBSI per 1000 catheter days; OR = 0.80; 95%, CI = 0.712-0.898; P < 0.001), and a lower CVC-related cost per day (€ 3.78 ± 4.45€ vs 7.28 ± 16.71; OR = 0.52; 95% CI = 0.504-0.535; P < 0.001) than patients with standard catheters, including 391 standard catheters during 1586 days of catheter and 245 CHSS impregnated catheters during 1685 days of catheter (35). Furthermore, we found that patients with CHSS in subclavian venous access showed a lower incidence of CRBSI (2.12 vs. 0 per 1000 days of catheter; P = 0.02) and lower CVC-related cost per day of catheter (€ 3.35 ± 3.75€ vs. 3.94 ± 9.95; PP = 0.002) than patients with standard catheters, including 518 patients with standard catheters during 3297 days, and 353 patients with CHSS impregnated catheters during 2743 days (36).

The use of antimicrobial impregnated catheters has been found to decrease the incidence of CRBSI and catheter-related costs as indicated by some cost-effectiveness analyses (13, 37, 38). The costs associated with the increase of hospital stay were included in all the cost-effectiveness studies, and this cost varied greatly between different studies. The mean additional cost associated with CRBSI was approximately $10000; however, in some studies that cost was as high as $40000 (4) and $71000 (6), mainly due to an increase in hospital stay of more than 20 days. The cost-effectiveness analyses carried out by our team were simpler than those previously published as we only compared the immediate catheter-related costs (which only included the cost of CVC, diagnosis of CRBSI and antimicrobials for the treatment of CRBSI, and did not include the costs due to increased hospital stay).

In a multi-centre RCT by Darouiche et al., including 382 first generation CHSS impregnated catheters and 356 rifampicin-minocycline impregnated catheters, it was found that patients with rifampicin-minocycline impregnated catheters had a lower rate of CRBSI than patients with first generation CHSS impregnated catheters (0.3% vs. 3.4 %; P < 0.002) (39). However, a comparison between rifampicin and second-generation CHSS impregnated catheters in the incidence of CRBSI has not been reported.

3.4. Recommendation of Guidelines for the use of Antimicrobial-Impregnated Catheters

The guidelines for the prevention of intravascular catheter-related infections, published in 2011, by the society of

critical care medicine (SCCM), infectious diseases society of america (IDSA), society for healthcare epidemiology of america (SHEA), surgical infection society (SIS), american college of chest physicians (ACCP), american thoracic society (ATS), american Society of critical care anaesthesiologists (ASCCA), association for professionals in infection control and epidemiology (APIC), infusion nurses society (INS), oncology nursing society (ONS), american society for parenteral and enteral nutrition (ASPEN), society of interventional radiology (SIR), american academy of paediatrics (AAP), Paediatric Infectious Diseases Society (PIDS), and the healthcare infection control practices advisory committee (HICPAC) of the centres for disease control and Prevention (CDC), recommended the use of an antimicrobial impregnated catheter (CHSS or rifampicin-minocycline impregnated catheter) in patients whose catheter is expected to remain in place for more than days and if the CRBSI rate has not decreased after implementation of a comprehensive strategy for its reduction (which should include at least the following three components: education of people who insert and maintain catheters, use of maximal sterile barrier precautions, and the use of a > 0.5% chlorhexidine preparation with alcohol for skin antisepsis during catheter insertion) (10).

However, there are some concerns associated with the published recommendations. First, the guidelines recommended the use of CHSS impregnated catheters based on three RCTs, which found a reduction on the incidence of catheter tip colonisation with the use of second-generation CHSS-impregnated catheters (14-16). However, in these guidelines the type of CHSS-impregnated catheters was not specified (first generation, second generation or both). Besides, significant differences were not found in the incidence of CRBSI with the use of second generation CHSS impregnated catheters in the three RCTs (14-16). In addition, the published meta-analysis by Hockenhull et al. (including three RCTs and reporting a lower risk of CRBSI with the use of second-generation CHSS impregnated catheters) was not mentioned in these guidelines (13). Second, the recommendations about the use of rifampicin-minocycline impregnated catheters in the guidelines were based on the findings of two RCTs showing that rifampicin-minocycline impregnated catheters reduced the risk of CRBSI (40, 41). However, the meta-analysis by Falagas et al. (17), including these two RCTs and another four RCTs, which found that rifampicin-minocycline impregnated catheters reduced CRBSI, was not mentioned in these guidelines. Besides, our published observational study reporting the reduction of CRBSI incidence with the use of RM impregnated catheters was not mentioned in these guidelines (18).

3.5. Bundles to Reduce Catheter-Related Bloodstream Infections

Previous studies have indicated that the implementation of a bundle for CRBSI prevention reduces the incidence of CRBSI (42-45). In the Keystone project by Pronovost et al., carried out between March 2004 and September 2005 in 103 intensive care units (ICU) in the Michigan state, it was found that the implementation of a bundle for CRBSI prevention reduced the median CRBSI incidence from 2.7 (mean of 7.7) infections per 1000 days of catheter to 0 (mean of 2.3) ($P \leq 0.002$) (42). After the Michigan experience, other clinical trials also reported a reduction in the incidence of CRBSI with the implementation of bundles, such as a Spanish study performed between April 2008 and June 2010 in 192 ICUs (43), a study from the United States on 29 paediatric ICUs (44), and another project with 12 United States ICUs (45). In the Spanish bacteremia zero (BZ) project, it was found that the median CRBSI rate decreased from 3.07 to 1.12 infections per 1000 days of catheter, after the implementation of a bundle for CRBSI prevention ($P < 0.001$). All these studies recommended similar measures for the prevention of CRBSI, including hand washing, the use of full-barrier precautions during the insertion of CVC, cleaning the skin with chlorhexidine, avoidance of the femoral site if possible, and removal of unnecessary CVC.

4. Conclusions

In conclusion, the use of antimicrobial impregnated catheters is an effective and efficient measure for the prevention of CRBI, and could be considered in some clinical circumstances associated with higher risks of CRBSI, such as patients with a CVC at the internal jugular venous site in the presence of tracheostomy or in the femoral venous site.

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