Bundle Approach to Reduce Bloodstream Infections in Neutropenic Hematologic Patients with a Long-Term Central Venous Catheter

Conjunto de Medidas Adotadas para Reduzir Infeções Sistémicas no Doente Hematológico em Neutropenia com Cateter Venoso Central de Longa Duração

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ABSTRACT

Introduction: The objective of the study was to reduce, by a bundle of interventions, the global bloodstream infections and catheter-related bloodstream infections rates in neutropenic hematology patients with a long-term central venous catheter.

Material and Methods: This was a non-randomized prospective study. It was conducted in a 20-bed hematology oncology unit (Portuguese Institute of Oncology, Porto, Portugal) between 1st of August 2010 and 31st of January 2012. In this period we introduced a bundle of interventions (study group) and compared the results with the six months prior to implementation (control group). The interventions consisted in the use of a neutral pressure mechanical valve connector instead of a positive pressure mechanical valve connector, a more frequent change of this connector and a more efficient clean solution. One hundred and sixteen hematology patients with a long-term central venous catheter at time superior of 72 h, with 8 867 central venous catheter days [6 756 central venous catheter days in the study group and 2 111 central venous catheter days in the control group] were included in the study.

Results: A significant reduction in bloodstream infections rates and catheter-related bloodstream infections rates was achieved. Bloodstream infections rates: [32.69 (control group) vs. 9.43 (study group)], incidence reduction 71% [relative risk 0.2886, CI 95% (0.1793 – 0.4647), $p < 0.001$] and catheter-related bloodstream infections rates: [17.53 (control group) vs. 4.73 (study group)], incidence reduction 71% [relative risk 0.2936, CI 95% (0.1793 – 0.5615), $p < 0.014$]. No significant difference ($p > 0.05$) was found in the neutrophil count at the time of blood culture samples between groups: 69% (< 500 neutrophils/mm^3) [71% (study group) vs. 68% (control group)].

Conclusion: The introduction of this bundle of interventions based on the variables of patient, product and practice, supported by the Healthcare and Technology Synergy framework, quickly resulted in a significant reduction of bloodstream infections and catheter-related bloodstream infections rates.

Keywords: Catheter-Related Infections; Catheterization, Central Venous; Neutropenia.

RESUMO

Introdução: O objetivo deste estudo foi reduzir através de um pacote de medidas as infeções sistémicas e as taxas de infeções com origem no cateter venoso central nos doentes hematológicos em neutropenia com cateter venoso central de longa duração.

Material e Métodos: Estudo prospetivo não randomizado realizado na unidade onco-hematológica do Instituto Português de Oncologia do Porto no período compreendido entre 1 de agosto de 2010 até 31 de janeiro de 2012. Durante este período foi introduzido um pacote de medidas (grupo estudo) e comparados os resultados nos 6 meses anteriores à sua implementação (grupo de controlo). As medidas consistiram na utilização de conectores de pressão neutra em detrimento dos conectores de pressão positiva, na sua troca mais frequente e numa solução anti-séptica mais eficaz. Foram incluídos neste estudo 116 doentes hematológicos com cateter venoso central de longa duração inserido por um período superior a 72 h. Foram contabilizados 8 867 dias de cateter (6 756 dias de cateter venoso central no grupo estudo e 2 111 dias de cateter venoso central no grupo de controlo).

Resultados: Obteve-se uma redução significativa nas taxas de infeções sistémicas e infeções com origem no cateter venoso central. As taxas de infeções sistémicas: [32,69 (grupo de controlo) *vs*. 9,43 (grupo estudo)], com uma redução de incidência de 71% [risco relativo 0,2886, CI 95% (0,1793 – 0,4647), $p < 0,001$] e taxas de infeções com origem no cateter venoso central: [17,53 (grupo de controlo) *vs*. 4,73 (grupo estudo)], com redução de incidência de 71% [risco relativo 0,2936, CI 95% (0,1793 – 0,5615), $p < 0,014$]. Não foi encontrada diferença significativa ($p > 0,05$) na contagem de neutrófilos à data da colheita das amostras de hemoculturas entre ambos os grupos: 69% (< 500 neutrófilos/mm^3) [71% (grupo estudo) *vs*. 68% (grupo de controlo)].

Conclusões: A introdução deste pacote de medidas baseado nas variáveis do paciente, produto e prática, suportado pela estrutura Healthcare and Technology Synergy, resultou numa redução significativa das taxas de infeções sistémicas e infeções com origem no cateter venoso central.

Palavras-chave: Cateterização Venosa Central; Infecções Relacionadas com Cateter; Neutropenia.

INTRODUCTION

In hematology departments, central venous catheters (CVC) are indispensable tools, allowing the administration of fluids, chemotherapy, antibiotics, blood products, parenteral nutrition and blood sampling. Patients diagnosed with

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hematological malignancies, especially acute leukaemia patients, have a greater risk of developing infections, due to the high incidence of prolonged and severe neutropenia (< 100 neutrophils cells/mm^3) secondary to chemotherapy. The use of a CVC strongly increases the risk of bloodstream infections in this kind of patients.[1]

The Healthcare and Technology Synergy (HATS) framework[2] highlights the importance of considering the interplay between patient, practice and product when evaluating the effectiveness of research, and therefore had practical applicability to this study design. Infection prevention strategies that incorporate an evaluation of the effectiveness of the product, as well as considerations of patient variables and nursing practice considerations, have improved success in reducing the risk of infection in patients requiring central vascular access devices.[2]

In these patients the best choice of product (e.g. the type of needleless connector) and practice (management of CVC) is fundamental to preventing and reducing the risk of bloodstream infections (BSI).[2] Products such as needleless connectors are proven to be significant variables in the development of BSI.[3,4]

To prevent the catheter related bloodstream infections (CRBSI) we need to: (1) reduce microorganism adhesion to the catheter and (2) prevent microorganism migration to bloodstream — a bundle approach offers the most comprehensive infection prevention strategy in the practice setting.

In short-term CVCs, the extraluminal origin (insertion site) of infection is the predominant mechanism, and the intraluminal route (catheter hub or needless connectors) predominates during the use of long-term CVCs, the most frequently used CVCs in hematology departments.[5]

Needleless connectors are devices used to facilitate the catheter manipulation and to protect health care workers from needle stick injuries.[6] The needleless connectors most commonly used nowadays can be with a split septum configuration or mechanical device with an internal valve, also known as mechanical valve connectors (MVC). Several reports showed that MVC are a special target for biofilm formation and it can increase CRBSI, some institutions reported an increase in BSI rate when MVC were introduced against the split septum needless connectors. The needleless connectors can induce a neutral, a positive or a negative pressure inside the catheter lumen.[7] Connectors with neutral pressure (NP-MVC) were the first to be introduced but they need a flush of heparin after each manipulation to decrease the rate of catheter occlusion. To decrease the use of heparin, connectors with positive pressure (PP-MVC) were developed and nowadays are widely used.[8] Manufacturers have shown the safety of PP-MVC concerning the rate of catheter occlusion when compared with NP-MVC; however, the safety of these devices concerning the infection risk were not analyzed and there have been several reports of increased CRBSI with their use.[9] There are reports in the literature of an increase in the rate of CRBSI when the NP-MVC were substituted for a PP-MVC, and a reduction to basal levels with the reintroduction of NP-MVC.[7] With the knowledge of this data we decided to introduce a bundle of four measures to reduce the risk of infection in our patients. Several strategies are recommended to reduce the risk of infection associated with the use of CVC.[10] Considering that biofilm formation is a key element in BSI risk, our hypothesis was that the introduction of a bundle of measures targeting both product and practice could result in a lower incidence of BSI, particularly in patients with a long-term CVC, frequently used in hematology.

MATERIAL AND METHODS

Selection and description of participants

This was a non-randomized prospective study. It was conducted in a 20-bed hematology oncology unit in the Portuguese Institute of Oncology (Porto, Portugal) between 1st of August 2010 and 31st of January 2012. In this period we introduced a bundle of interventions (study group) and compared the results with the six months prior to implementation (control group). The sample included all consecutive adult (+ 18 years) patients admitted at our department with the diagnosis of acute leukemia (AL), non-Hodgkin's lymphoma B (NHL-B), and multiple myeloma (MM), using a long-term CVC for a time period of at least 72 h, undergoing chemotherapy treatment or during the aplasia phase.

All the CVCs were long-term tunnelled Hickman-type catheters without any antimicrobials, inserted in the subclavian vein, with double (7 Fr) or single lumen (6 Fr). No prophylactic antibiotics other than co-trimoxazole (for *Pneumocystis jirovecii*) and itraconazole were used. CVCs were used for fluid administration, chemotherapy, blood product transfusions, parenteral nutrition when needed, and for collection of blood samples most days. All patient rooms are equipped with positive pressure ventilation and HEPA® filters, and when patients are neutropenic visitor restrictions are instituted. During the study period, no other relevant departmental changes were implemented, including CVC insertion procedures, the indication for blood cultures, the process of blood cultures, the antibiotic use policy, or the nursing team number and composition.

Technical information

The bundle of interventions introduced comprised the following:

- Product: substitution of PP-MVC (Autoflush, Vygon®) in use at our department during a long period of time by a NP-MVC (Bionecteur, Vygon®).
- Practice: changing the needleless connector twice a week instead of once a week.
- Practice: changing the needleless connector after each sample of blood cultures to study a new episode of fever.
- Product: replacement of alcohol 70% solution for the chlorhexidine 2% in alcohol 70% solution to clean the needleless connector.

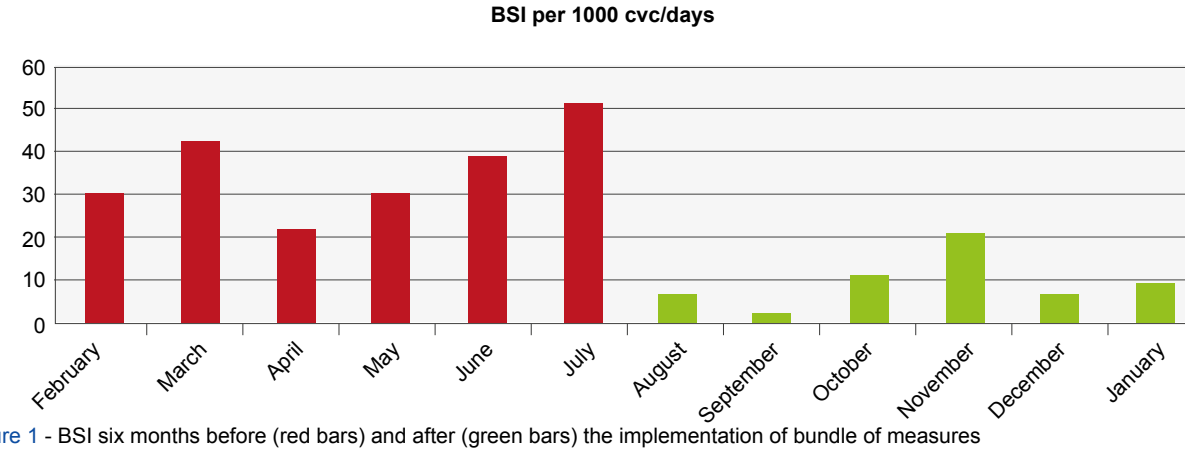

Figure 1 - BSI six months before (red bars) and after (green bars) the implementation of bundle of measures

Blood cultures collection

The indication for blood cultures include: the presence of fever (temperature ≥ 38.3ºC or temperature ≥ 38ºC persisting for more than one hour) or, in the absence of fever, the presence of other signs of infection.[11] After the collection of blood cultures all the patients started a large spectrum antibiotic and if 72 hours after the first blood cultures the fever persisted or recurred with or without other signs of infection a new set of blood cultures were obtained. Blood culture samples were collected first from a peripheral vein followed by sampling from CVC lines with only a few minutes separating them. CRBSI was considered if samples collected from CVC lines were positive and peripheral vein negative, or when samples collected from CVC lines became positive 120 minutes or more before samples from peripheral vein, known as differential time to positivity (DTP).[12]

Statistics

Categorical variables are presented as frequencies (n) and percentages (%). All *p* values reported are based on two-tailed tests of significance χ2. A *p* value less than 0.05 was considered to be statistically significant. The data was analyzed using SPSS Statistics for Windows (SPSS Inc., Version 17.0). All data was treated in compliance with the Portuguese law, according to Law n º 67/98 of 26 October concerning the protection of personal data.

Table 1 - Control *vs*. Study group: BSI and CRBSI risk reduction

	ALL BSI	CRBSI
Control Group	32.69	17.53
Study Group	9.43	4.73
Relative Risk	0.2886	0.2936
CI 95%	[0.1793; 0.4647]	[0.1535; 0.5615]
Incidence Reduction	71%	71%
p	< 0.001	< 0.014

RESULTS

One hundred and sixteen patients [62 AL, 39 NHL-B, 15 MM] using a long-term CVC were included with a total of 8 867 CVC days [6 756 CVC days (study group) and 2 111 CVC days (control group)]. A significant reduction in BSI (Fig. 1) rates and CRBSI rates was achieved. BSI rates: [32.69 (control group) vs. 9.43 (study group)], incidence reduction 71% [relative risk 0.2886, CI 95% (0.1793 – 0.4647), $p < 0.001$] and CRBSI rates: [17.53 (control group) *vs*. 4.73 (study group)], incidence reduction 71% [relative risk 0.2936, CI 95% (0.1793 – 0.5615), $p < 0.014$] (Table 1). The neutrophil count at the time of blood culture sampling showed that in 69% of the episodes the patient had less than 500 neutrophils per mm^3. No significant differences were found between study and control groups, [71% (study group) vs. 68% (control group); p>0.05).

Bloodstream infections and blood cultures collection

The total number of blood cultures collected was 696 [475 (study group) corresponding to 69 blood cultures/1 000 CVC days, and 225 (control group) corresponding to 106 blood cultures/1 000 CVC days). This represents a 35% reduction in the number of blood cultures collection in the study group. The decrease in the number of collected blood cultures was also associated with a significant decrease in the number of positive blood cultures. The total number of positive blood cultures was 139 [64 (study group) and 75 (control group)].

Microorganism recovered

We analyzed the number of microorganism recovered six months before and six months after the bundle introduction. There was a more pronounced reduction in gram-positive bacteria compared to gram-negative (95% vs. 41.4%) (Fig. 2). *Staphylococcus epidermidis* (94.5%), *Pseudomonas aeruginosa* (90%) and *Escherichia coli* (72.2%) were the microorganisms with the biggest reduction (Table 2). Following the bundle introduction only the *Klebsiella pneumoniae* microorganism increased (88.8%); however, in analyzing the origin of these infections we found that only 2 of the 9 cases were considered CRBSI. No blood cultures were positive for fungi.

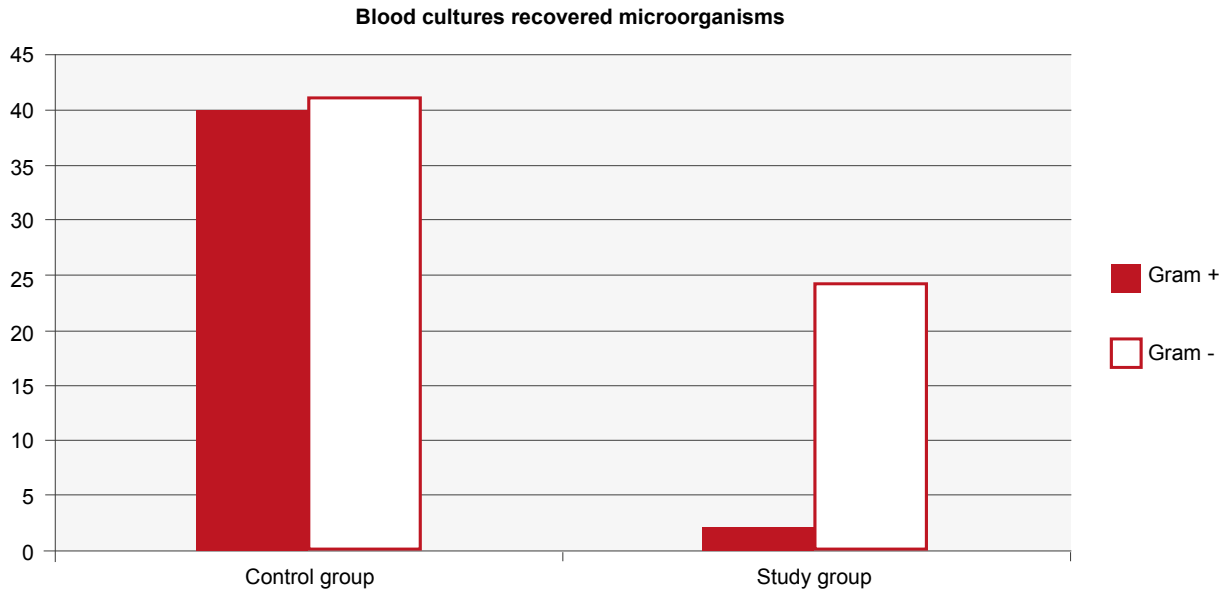

Figure 2 - Type of recovered microorganisms in blood cultures of control and study groups six months before (red bars) and after (white bars) the implementation of a bundle of measures

Table 2 - Microorganism recovered six months before/after the bundle implementation

Microorganism Recovered (n) (%)	Before bundle Introduction	After bundle Introduction
Gram-positive	40 (49.4)	2 (7.7)
Staphylococcus haemolyticus methillin-resistant	3 (7.5)	0 (0)
Staphylococcus hominis	2 (5)	0 (0)
Staphylococcus hominis methililin-resistant	1 (2.5)	0 (0)
Staphylococcus epidermidis	18 (45)	1 (50)
Staphylococcus haemolyticus	7 (17.5)	0 (0)
Staphylococcus parasanguinis	1 (2.5)	0 (0)
Staphylococcus mitis	6 (15)	1 (50)
Staphylococcus lugdunensis	1 (2.5)	0 (0)
Staphylococcus sanguinis	1 (2.5)	0 (0)
Gram-negative	41 (50.6)	24 (92.3)
Escherichia coli	18 (43.9)	5 (20.8)
Pseudomonas aeuroginosa	10 (24.4)	1 (4.2)
Acinetobacter baumannii	1 (2.4)	0 (0)
Enterococcus faecalis	5 (12.3)	2 (8.3)
Enterococcus Faecium	3 (7.3)	2 (8.3)
Stenotrophomonas (X.) *malthopilia*	1 (2.4)	0 (0)
Enterobacter cloacae	2 (4.9)	1 (4.2)
Klebsiella Pneumoniae	1 (2.4)	9 (37.4)
Proteus Mirabillis	0 (0)	1 (4.2)
Enterobacter espécies	0 (0)	1 (4.2)
Burkholderia (P.) *picketti*	0 (0)	1 (4.2)
Total	81	26

DISCUSSION

Hematology patients are at a very high risk of BSI with the use of a long-term CVC because they frequently have severe neutropenia and have the CVC in place for a long time. The true incidence of BSI in these patients is not well known because the research in this field is very scarce.[13] In our study, 71% (study group) and 68% (control group) of the patients were neutropenic at the time of blood sample collection.

The BSI rates registered in both groups were higher than in previous reports, which we attribute to the fact that most of the published work has been done in intensive care units, where patients are rarely neutropenic and usually use short-term CVC.[14] If we considered all the positive blood cultures and not only those potentially linked to CVC, the BSI rate in this study is higher than other reports; however, if we use the DTP method the numbers were significantly lower.[15] DTP is considered a good method to determine the source of infection.[16]

Bundle Adopted

The use of a CVC, both short-term and long-term, is a well recognized risk factor for healthcare-associated BSI, and much effort has concentrated on reducing this risk. We tested the hypothesis that the implementation of a bundle of measures that could contribute to a reduction in the biofilm formation would reduce the rate of BSI in this population.[17]

Recent reports concerning the utilization of MVC showed that the use of PP-MVC was implicated in an increase in the number of BSI, and suggested that one of the reasons could be a greater propensity of PP-MVC to form biofilm.[9] We therefore decided to change from a PP-MVC (Autoflush, Vygon®) to a NP-MVC (Bionecteur, Vygon®). A theoretical explanation for the higher BSI risk with PP-MVC can be the more complex mechanical design of the internal valve, and the increase in the dead space which cannot be cleaned with routine flushing.

Some data suggests that the connector biofilm forms after the first 72 h of use.[9] Considering this, in addition to the use of NP-MVC we also decided to change the needleless connectors twice a week instead of once a week, as the indication of producer, and also to change the needleless connector after each collection of blood cultures to study a new episode of fever or the persistence of fever for more than 72 h. knowing that a misture of chlorhexidine 2% in alcohol 70% solution is more effective in gram positive microorganism and that these agents are more prevalent in BSI related to CVC we choose this solution in substitution of iodopovidona solution to clean the needleless connector in our high risk patients (immunocompromised patients).[17,18]

At our hands the implementation of the bundle of four simple measures resulted in a significant reduction in the rate of BSI.

Microorganism recovered

Coagulase-negative staphylococcus (CoNS), *Staphylococcus aureus*, *Pseudomonas aeruginosa* and enteric gram-negatives are considered to be the most common microorganisms involved in CRBSI.[19] In our study we saw a strong reduction in the number of these microorganisms.

Methicillin resistant microorganisms are one of the most frequent microorganisms transmitted between health-care workers and patients. The implementation of measures to reduce the risk of transmission is fundamental to patient care.[20] In our study, there was no isolation of drug-resistant pathogens like methicillin resistant *S. aureus* in either group.

Scope and limitations

As we decided to implement simultaneously all the possible measures that would contribute to the reduction in BSI and CRBSI, we are unable to determine which of the measures was the most effective. Also very important to us was the fact that the impact of the measures persisted after the end of the study. Two years after the introduction of the bundle, the rate of healthcare-associated BSI and CRBSI has remained constant.

CONCLUSION

Evidence-based nursing staff management of CVCs is the key to prevent and reduce the impact of BSI and CRBSI in the neutropenic hematology patient. The introduction of this bundle of interventions, with emphasis in the use of a NP-MVC in detriment of the use of a PP-MVC, associated with a more frequent change of the connector and an appropriate clean solution, based on the variables of the patient, product and practice, supported by the HATS framework, quickly resulted in a significant reduction of BSI and CRBSI rates, and we suggest that this approach should be adopted in the management of patients with a long-term CVC.

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PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

All data was treated in compliance with the Portuguese law, according to Law n º 67/98 of 26 October concerning the protection of personal data.

CONFLICTS OF INTEREST

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

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