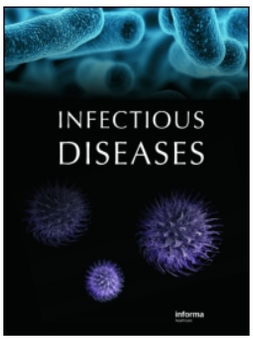

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BRIEF REPORT

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Equal effect of vancomycin lock with or without heparin in treatment of central venous catheter related blood stream infections – an observational study in palliative home care

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ABSTRACT

Background: Catheter related blood stream infections is a complication in patients with central venous catheter. The aim of this study was to compare vancomycin-heparin-lock and non-heparin, high-dose vancomycin-lock as treatment in patients admitted to palliative home care. With non-heparin, high-dose vancomycin-lock a high concentration of 5 mg/mL vancomycin is attained instead of only 500 ug/mL when dissolved in heparin. The non-heparin method also has the advantage of being easier and cheaper but might entail an increased risk of clotting.

Methods: Medical records from patients enrolled at a palliative home care unit in Stockholm between 2016 and 2018 were reviewed retrospectively. Three divisions used vancomycin-heparin-lock and the other 3 divisions used non-heparin, high-dose vancomycin-lock. Inclusion criteria were a central venous catheter related blood stream infection treated with one of the two methods for >7 days and a follow-up blood culture at the end of treatment.

Results: Twenty-five patients fulfilled the inclusion criteria, 12 treated with vancomycin-heparin-lock and 13 with non-heparin, high-dose vancomycin-lock. There was no significant difference in resolved infections between the two treatments, 6 of 12 for vancomycin-heparin-lock and 10 of 13 for non-heparin, high-dose vancomycin-lock ($p = .23$). In the non-heparin group one central venous catheter was removed due to clotting although the infection had resolved. Overall, removal of central venous catheter was similar in the two groups (6 of 12 and 4 of 13, $p = .43$).

Conclusion: The current study does not support superiority of one treatment over the other. However, larger, randomized studies are needed, before firm conclusions can be drawn.

Abbreviations: CRBSI: Catheter related blood stream infections; CVC: Central venous catheter; PICC: Peripherally inserted central catheter; VAP: Subcutaneous venous access port

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Introduction

Infections with coagulase-negative *staphylococci* (CoNS) is a complication in patients with central venous catheter (CVC) leading to Catheter related blood stream infections (CRBSI) [1,2].

CRBSI with CoNS is usually treated with vancomycin infusions 1–2 times/day. A vancomycin-heparin-lock can be injected in the CVC between infusions. There are only a few clinical studies evaluating vancomycin-heparin-lock for treatment of CRBSI [3–6]. Although the evidence for using vancomycin-heparin-lock is sparse it is still a routine method in most units treating cancer-patients.

An alternative to vancomycin-heparin lock is not to flush the CVC after vancomycin infusion and leave the last millilitre of the infusion solution in the CVC. This gives a high concentration of vancomycin (5 mg/mL) but without heparin. This method is referred to as non-heparin, high-dose vancomycin-lock from here on. A possible risk with this method is clotting of the catheter, making it unusable.

In vitro studies show that higher concentrations of vancomycin, up to 5 mg/mL, give better bactericidal effect against bacteria in biofilms present in the catheter [7,8]. Such high concentrations of vancomycin cannot be dissolved in heparin due to low pH, which causes precipitation of vancomycin. The highest concentration of vancomycin to be solved safely in heparin is 0.5 mg/mL [9].

According to the current Swedish recommendations on CVC infections both methods (with and without heparin), are recommended, although there are no published studies comparing the two methods in a clinical setting.

In the Stockholm region, advanced medical home care teams (ASIH) offer hospital-like palliative and supportive care at home to oncological and non-oncological patients. Many patients enrolled in the home care teams are encouraged to have a CVC to gain a safe, accessible route for treatments, parenteral nutrition, and fluid and blood-transfusions when needed. A previous study at our medical home care unit in Stockholm showed a high prevalence of CRBSI in patients receiving parenteral nutrition at home [2].

To our knowledge no previous studies comparing the two vancomycin-lock methods have been carried out in late-stage palliative care patients.

The aim of this study was to compare the efficacy and safety of treatment CVC-infections with vancomycin-heparin-lock and non-heparin, high-dose vancomycin-lock, in palliative care patients. We performed a retrospective study at our medical home care unit in Stockholm, Sweden, where half of the unit used one method and the other half the other method.

Method

Study population

An observational, retrospective study was performed to compare two vancomycin treatments, with or without heparin lock, when treating CRBSI. Medical records of all 2364 patients enrolled at an Advanced Medical Home Care Unit in Stockholm, at any time during 2016–2018 were reviewed and we found 1158 patients with a CVC. This cohort was used for the present study.

The Unit comprises 6 medical home care divisions covering different geographical areas in the southern part of Stockholm. The unit is described in detail previously [10]. Each division has 60–65 patients enrolled on a given day and has a median admission time of 4 months, ranging between days to years. In 2016 three divisions were assigned to use the vancomycin-heparin-lock and the other three divisions to the use the non-heparin, high-dose vancomycin-lock.

All patients at the unit were treated with the same CVC line care protocol, in accordance with the Swedish national guidelines on CVC care. This includes flushing the line with at least 20 mL NaCl solution before and after all drug administrations and flushing the line with 40–60 mL NaCl solution after administration of parenteral nutrition. However, after administration of vancomycin no flushing was done in non-heparin, high-dose vancomycin-lock method. Instead, the last mL of the infusion (vancomycin 5 mg/mL in saline) was left in the CVC.

For the systemic administration of vancomycin, plasma concentration measurements were performed in all patients regularly and doses adjusted accordingly. Thus, all patients had an individualized daily dose of the systemic vancomycin.

Inclusion criteria

The inclusion criteria were: a CRBSI as defined below which was treated with either vancomycin-heparin-lock or non-heparin, high-dose vancomycin-lock for at least 7 days and a follow-up blood culture was collected after treatment.

If the lock method was changed during the treatment period the patient was excluded.

Data on resolved CVC infections (as defined below), treatment time, result of the follow-up blood culture, possible adverse events due to treatment and removal of CVC was collected.

A patient could only be included once in the analysis and only the first CVC infection full-filling the inclusion criteria was included.

Definition of CRBSI

In order to identify patients with CRBSI, all blood cultures in the study population were screened. CRBSI was diagnosed according to previous guidelines [11,12]: (1) Fever or clinical signs of infection; (2) Detection of significant counts of the same microorganism in a peripheral blood culture as in a culture from the central venous access insertion site or from the tip of the CVC; (3) Detection of significant amount of the same microorganism in a blood culture from the central venous access as in a peripheral culture, where the central culture should be positive at least two hours ahead of the peripheral culture; (4) No other obvious source of infection should be present.

Outcome: resolved infection or removal of CVC

The CVC infection was defined as being resolved if the follow-up blood culture was without bacterial growth and the CVC could be used again. The follow-up time for removal of CVC was 3 months or until death if earlier than 3 months after the CVC-infection.

Ethical considerations

The study protocol was approved by the Central Ethical Committee in Sweden, Dnr 2019/01110. This was a retrospective review of medical records in patients admitted to palliative care and all included patients are now deceased. No written informed consent was needed from next-of-kin according to the Ethical Committee.

Statistical analysis

Statistical analysis was performed using Graph-Pad Prism version 8.0. Un-paired, two-sided *t*-test was used to analyse continuous variables and Fisher's exact test for categorical variables. A p-value $<.05$ was considered statistically significant.

Results

Of the 1158 patients with a CVC, 63 had CRBSI treated with vancomycin during the study period. Twenty patients were excluded due to treatment with vancomycin $<$ 7 days, 10 had lack of follow-up data, and in 8 the vancomycin-lock method was changed during the treatment period. Finally, 25 patients full-filled the inclusion criteria for this study. Twelve were treated with vancomycin-heparin-lock and 13 with non-heparin, high-dose vancomycin-lock. A flow-chart of included patients is presented in Figure 1.

Of 25 included patients, 22 were admitted to medical home care due to advanced cancer disease in need of palliative care. Three patients had non-oncological conditions in need of supportive care (ALS, respiratory insufficiency and severe cerebral palsy).

The mean treatment time in the two groups were 12 and 13 days (Table 1). The CVC infections resolved in 6 of 12 patients (50%) in the vancomycin-heparin-lock group. Time to control culture was performed at least 2 days after end-of-treatment. No adverse effects of treatment were reported in this group, but the CVC was removed due to unresolved infection in 6 of 12 patients (Table 1).

Ten of 13 CVC infections resolved in the non-heparin, high-dose vancomycin-lock group (Table 1). In one case the CVC clotted at the end of treatment and had to be removed. One patient experienced acute renal insufficiency (estimated GRF 22 mL/min) probably due to high serum concentrations of vancomycin. Renal function returned to normal after vancomycin treatment was terminated. The CVC was removed and considered as still infected at the time of removal.

Discussion

In this study we show that leaving high-vancomycin (5 mg/mL) solution without heparin in the CVC is as effective and safe as the common vancomycin-heparin-lock in palliative care patients. There were no significant differences between the groups in resolved CVC infections and in adverse events. Both treatments had a high rate of removal of the CVC (30–50%), due to unresolved infections and to adverse effects of vancomycin treatment.

A recent study on vancomycin-lock for CVC-infections showed similar results with a success rate of 40–70% when treating CVC infections [13]. In a systematic review on studies on prevention of CRBSI using different antibiotic locks in cancer patients, the authors concluded

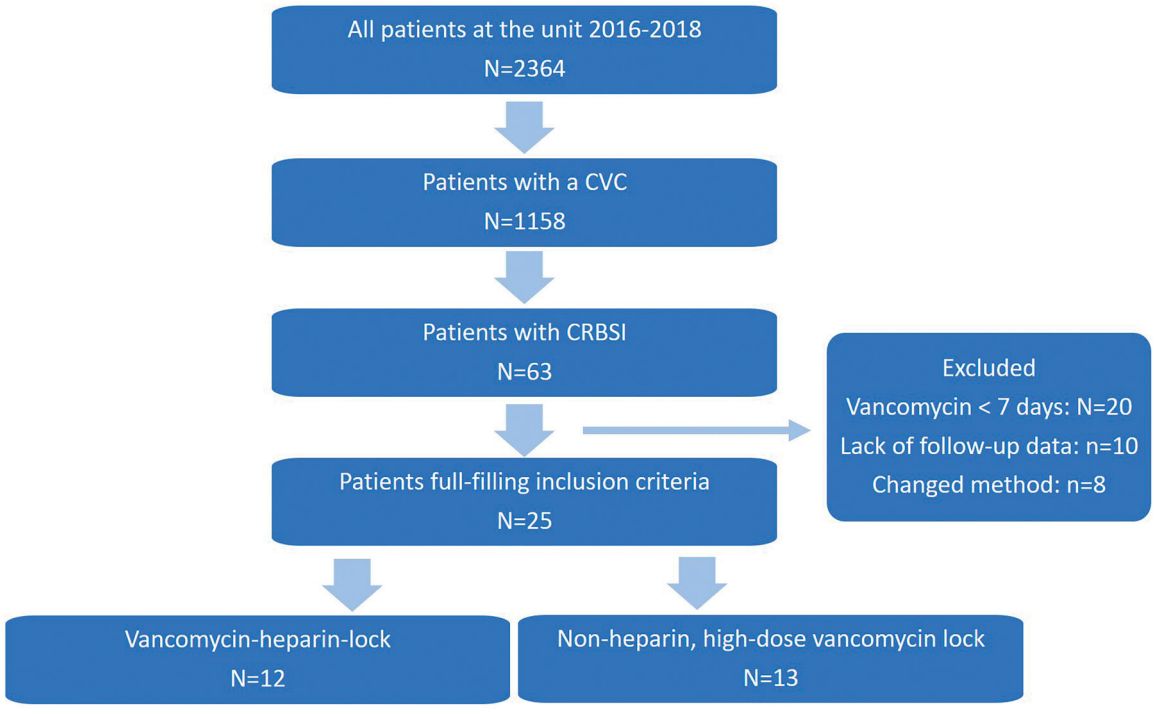

Figure 1. Flow-chart of included and excluded patients in the study cohort. CVC: central venous catheter; CRBSI: Catheter related blood stream infections.

Table 1. Comparison of two treatments of infections in central venous catheter (CVC) in patients admitted to palliative home care: (1) the heparin-lock method with vancomycin 0.5 mg/mL or (2) non-heparin, high-dose vancomycin-lock (5 mg/mL).

	Vancomycin-heparin-lock, 0.5 mg/mL ($n = 12$)	Non-heparin, high-dose vancomycin-lock, 5 mg/mL, ($n = 13$)	*p-value*
Male (n)	4	6	.69
%	(33%)	(46%)	
Age, mean	69 years	63 years	.23
(min-max)	(62–82)	(21–78)	
Cancer diagnosis	11	11	1.00
	(92%)	(85%)	
Treatment time, mean	13 days	12 days	.31
(min-max)	(7–17)	(7–16)	
Time to blood culture after treatment, mean (range)	7 days	7 days	1.00
	(2–16)	(2–15)	
Resolved Infections after treatment, n (%)	6	10	.23
	(50%)	(77%)	
CVC had to be removed	6	4	.43
n (%)	(50%)	(31%)	
Adverse effects possibly associated with treatment	0	2*	.48
	(0%)	(15%)	

*One patient experienced reversible renal failure probably due to high serum concentrations of vanocymycin. One patient had occlusion in the CVC which had to be removed. Statistical analysis was performed with Fishers exact text or un-paired *t*-test when applicable.

that lock therapy may prevent CVC infections but there was not sufficient evidence to recommend a specific method [5].

Since three divisions were assigned to use one method and three the other method the study design can be described as 'pseudo-randomized'. However, it cannot be excluded that different routines at the six division could have affected the results. Moreover, the retrospective design does not rule out that the populations differed with regard to other and unknown factors, that could have influenced the results.

The major limitation of this study is the small sample-size, which increases the risk for both type 1 and type 2 errors. Still, this is the first study comparing vancomycin-heparin-lock with non-heparin, high-dose vancomycin-lock to treat CVC infections. It is also the first study evaluating vancomycin-lock treatment in palliative care patients. The results showed, surprisingly, that the non-heparin, high-dose vancomycin-lock was at least as effective and safe as the vancomycin-heparin-lock. The expected clotting of the CVC was only observed in 1 of 13 patients and the overall removal of CVC was similar

in the two groups. The non-heparin, high-dose vancomycin-lock has the advantage of being easier and cheaper than the vancomycin-heparin-lock. Too high serum concentrations of vancomycin may lead to renal failure [14,15]. One patient in the non-heparin, high-dose vancomycin-lock group developed renal failure probably due to too high vancomycin exposure, while there were no adverse events in the vancomycin-heparin-lock group. However, this was most likely due to infusion of a too high dose and not to the vancomycin lock.

The current study is only a small, observational study and larger, randomized studies are needed, before firm conclusions can be drawn. However, the current study does not support superiority of one treatment over the other.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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