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ORIGINAL ARTICLE

Experience of the use of lock therapy in pediatric patients with central venous catheter

Experiencia del uso de terapia de sello en pacientes pediátricos con catéter venoso central

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What do we know about the subject matter of this study?

Central venous catheters are essential in the care of children with chronic diseases, prolonged treatment, and limited venous access. In the case of bacteremia, therapeutic lock allows sterilization of the catheter lumen preventing its removal.

What does this study contribute to what is already known?

We were able to demonstrate a high rate of catheter preservation with the use of therapeutic lock, highlighting infections by pathogens in which the guidelines usually indicate its removal, and in oncological patients (implanted port) and with neutropenia. With prophylactic therapeutic lock (70% ethanol) the catheter was preserved in 2/3 of the patients.

Abstract

Lock therapy is useful for preserving indwelling catheters. Few lock therapy studies have been published in Latin America. **Objective**: To describe the clinical characteristics of pediatric patients using therapeutic and prophylactic lock therapy for six years in a high-complexity hospital in Colombia. **Patients and Method:** Cross-sectional descriptive study of patients aged < 18 years who received lock therapy. Collected variables included demographic data, clinical characteristics, blood test results, therapeutic interventions, frequency of admission to the pediatric critical care unit, and mortality. Descriptive analysis was performed. **Results:** 54 patients were included in the study, most of them males, with 67 episodes of therapeutic lock therapy use. The most frequent diagnosis was hematological neoplasm (61%). Among these patients, 88% presented neutropenia while receiving lock therapy. Catheter preservation was achieved in 75% of the cases. Aminoglycosides were the most commonly

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used antibiotics (38%). Mortality due to catheter-related bacteremia was 6%. Catheter preservation using ethanol solution 70% was achieved in 62% of the patients with prophylactic lock therapy, all of whom had chronic gastrointestinal pathology. **Conclusion**: Catheter preservation rates were 75% and 62% in patients with therapeutic and prophylactic lock therapy, respectively, with a higher rate achieved among cancer patients with neutropenia (80%). Aminoglycosides and vancomycin were the most commonly used antibiotics.

Introduction

Central venous catheters have become a critical component in the care of chronically ill children who require prolonged treatment and in whom venous access is difficult and very limited. Central venous access is very helpful in these patients, although not free of risks such as infections. Catheter-related bloodstream infection (CRBSI) is a pathology that increases morbidity and mortality, hospital stay, and costs. Comorbidities, the duration and type of central venous catheter (CVC), the insertion site, the experience of the person inserting the catheter, the use of total parenteral nutrition (TPN), and the number of catheter manipulations per day are some of the risk factors for the development of CRBSI[1].

For several decades, therapeutic lock has been described in CRBSI prevention and treatment guidelines and in other studies reported in the literature as a measure to sterilize the catheter lumen and prevent its removal[2-4]. It consists of filling the catheter lumen with a high concentration of antibiotic or antiseptic solution such as 70% ethanol, and leaving this solution for a period while the catheter is inactive, seeking to maximize bactericidal activity and penetration of the biofilm. The solutions that have been used are, among others, 70% ethanol and some antibiotics such as amikacin, gentamicin, vancomycin, cefazolin, and ciprofloxacin. Therapeutic lock has two indications: as treatment of identified CRBSI or prophylaxis with 70% ethanol to prevent CRBSI, the latter being more frequent in NPT users with intestinal failure. There are several studies in the literature on populations at high risk of infection such as oncology patients, neonates, hemodialysis patients, and intestinal failure, with documented benefit[1,5,6].

In our institution, therapeutic lock has been performed since 2012, following a standardized protocol. Few studies have been performed in Latin America regarding this therapy. The objective of this study was to describe the clinical characteristics of patients and episodes of CRBSI with therapeutic lock and its characteristics in pediatric patients for 6 years in a high-complexity Hospital in Colombia.

Patients and Method

Observational cross-sectional retrospective study. Patients under 18 years of age admitted to *Hospital Pablo Tobón Uribe* (Medellín) with a diagnosis of CRBSI that required the use of therapeutic lock and those to whom prophylactic therapeutic lock with 70% ethanol was administered between 2012 and 2018 were included. Patients with peripherally inserted central catheter (PICC) were excluded since therapeutic lock is not administered in these cases according to the institutional protocol and patients with incomplete information for analysis. *Hospital Pablo Tobón Uribe* is a high-complexity hospital in Medellín, Colombia, which has 78 pediatric hospitalization beds, an emergency department, and 27 critical care and neonatal beds.

Patients were identified through the medical indication for therapeutic lock in the clinical history. The information was collected in an Excel® database created by the researchers for this purpose. The variables studied were demographic (age and sex), clinical variables such as diagnosis, type of therapeutic lock, type of catheter, date of insertion and withdrawal, the medical specialty that inserted the catheter, therapeutic lock medication, catheter preservation, admission to the pediatric intensive care unit (PICU), death, among others.

Definitions

Catheter-related bloodstream infection: bloodstream infection in a patient with no other source of infection to explain the bacteremia, with paired blood cultures collected through the peripheral vein and catheter, presenting growth of the same microorganism and with a differential time-to-positivity greater than 120 min in the culture collected from the catheter[2].

Infection-free days in patients with prophylactic therapy were considered from the day of initiation of therapeutic lock until removal of the CVC due to its infection.

CRBSI-related mortality was defined as death from septic shock in patients with identified CRBSI with no other cause of infection.

Institutional protocol for therapeutic lock: the protocol was created in 2012 by the institution's pediatric infectious disease group. It has been defined that therapeutic lock in case of CRBSI should always be administered with systemic antibiotic, with a duration of 10 to 14 days, the catheter should not be used during this therapy, and control blood cultures should be performed 48 hours after initiation to evaluate the clearance of bacteremia and 48 hours after completion of this therapy to evaluate its success; in any of the cases, if one or two blood cultures are positive, the CVC should be removed. The volume of therapy is defined according to the size and type of catheter (single-lumen catheter 4.2 Fr: 1 ml; double-lumen catheter 5.0 Fr: 0.5 ml proximal route and 1 ml distal route; implantable port 4.5 Fr: 2 ml; implantable port 6.5 Fr: 3 ml) and its duration in the lumen should be at least 2 hours. The concentrations of the antibiotics used for the lock were as follows: amikacin 5 mg/ml, ampicillin 10 mg/ml, cefazolin 10 mg/ml, ciprofloxacin 0.2 mg/ml, gentamicin 5 mg/ml, vancomycin 5 mg/ml, and ethanol 700 mg/ml. Heparin is added to these solutions at 100 IU/ml, except for amikacin and ethanol, due to incompatibility.

The indications for prophylactic ethanol therapeutic lock are patients with intestinal failure or oncologic disease with limited vascular access, long-term catheter carriers, and those older than 1 month of life and weighing more than 5 kilos. Follow-up of patients with prophylactic therapy with 70% ethanol was during hospitalization since most patients are discharged with this therapy.

In cases where there is no return through the catheter and the lock cannot be removed, therapy should be suspended because of the risk of anticoagulation due to the heparin contained in the solution, and an evaluation by the infectious diseases group should be requested.

Statistical analysis

A descriptive analysis of all variables was performed. Qualitative variables are presented as frequencies or proportions and quantitative variables as medians and interquartile ranges according to their distribution by the Shapiro-Wilk test. Statistical analyses were performed using SPSS version 20 software.

The study was approved by the ethics committee of the *Hospital Pablo Tobón Uribe*.

Results

The results are described below in two sections, patients who received therapeutic lock for therapeutic purposes and for prophylactic purposes.

Therapeutic lock

67 episodes of therapeutic lock use were included in the study, occurring in 54 patients, most were males. The age range was from 1 month to 15 years. The most frequent diagnoses were hematological malignancies such as acute lymphoblastic leukemia (ALL), acute myeloid leukemia, promyelocytic leukemia, Burkitt leukemia, bilineal leukemia, and mixed lineage leukemia, followed by patients with intestinal failure and other tumors such as medulloblastoma, neuroectodermal tumor, and osteosarcoma. Table 1 shows the demographic and clinical characteristics of the patients.

Overall mortality accounts for 9 children (16%) and 3 (6%) had CRBSI-associated mortality, two of these with a diagnosis of ALL and one with intestinal failure. Table 2 describes the detailed characteristics of these patients.

Therapeutic lock characteristics

The median duration of the therapeutic lock was 10 days, ranging from 7 to 14 days. Table 3 shows the characteristics of the therapeutic lock in all episodes.

Of the 33 episodes in patients with hematologic malignancy, 29 (88%) had neutropenia at the time therapeutic lock was performed, all with implantable ports. Of the 40 episodes in patients with neoplastic disease, the catheter was preserved in 32 patients (80%).

All patients received concomitant systemic antibiotic therapy directed to the isolated microorganism.

Table 1. Demographic and clinical characteristics of patients

Characteristics	
Therapeutic lock therapy	n = 54
Age (years), median (IQR)	4 (1 - 9)
Male sex, n (%)	34 (63)
Diagnostic, n (%)	
Hematologic neoplasm	33 (61)
Intestinal failure	8 (15)
Solid tumors	7 (13)
Esophageal atresia	2 (4)
Others[a]	4 (7)
Catheter-related bloodstream infection mortality, n (%)	3 (6)
Prophylactic lock therapy	n = 7
Age (months), median (IQR)	7 (5 - 12)
Male sex, n (%)	5 (71)
Diagnostic, n (%)	
Intestinal failure	6 (86)
Congenital chronic diarrhea	1 (14)
Catheter-related bloodstream infection mortality, n (%)	0

IQR: interquartile range. [a]Others: food allergy (2 patients), autoimmune encephalopathy (1 patient), West syndrome (1 patient), myelodysplastic syndrome (1 patient).

Table 2. Characteristics of deceased patients who received therapeutic lock therapy

Characteristic	Patient 1	Patient 2	Patient 3
Age (years)	14	15	2
Sex	Male	Male	Male
Diagnostic	ALL	ALL	Intestinal failure
CRBSI microorganism	*Klebsiella pneumoniae*	*Escherichia coli*	*Staphylococcus epidermidis*
Lock therapy length	10 days	10 days	10 days
Lock therapy drug	Amikacin	Amikacin	Ethanol
Systemic antibiotic	Piperacillin-tazobactam	Aztreonam	Vancomycin
Catheter type	Implanted catheter	Implanted catheter	Broviac catheter
Observations	Palliative care		

ALL: Acute lymphocytic leukemia; CRBSI: Catheter-related bloodstream infection.

Table 3. Characteristics of therapeutic lock therapy

Characteristic	n = 67 n (%)
Catheter insertion	
Surgery	36 (54)
Interventional radiology	26 (39)
Unknown	5 (7)
Catheter preservation	50 (75)
Catheter type	
Implanted catheter	54 (81)
Broviac catheter	13 (19)
Drug lock therapy	
Aminoglycosides (Amikacin/Gentamicin)	25 (38)
Vancomycin	23 (34)
Ethanol	8 (12)
Cefazolin	7 (10)
Ampicillin	2 (3)
Ciprofloxacin	2 (3)
Critical care admission	17 (25)

Microorganisms isolated in blood cultures

Catheter preservation was achieved in 6 patients with *S. aureus* infection, one with *B. cereus*, and one with *P. aeruginosa* (15%). Table 4 shows the most frequently reported microorganisms in the blood cultures of 67 episodes, 7 (10%) of which presented polymicrobial infection (isolation of two microorganisms).

Three patients presented infection by *Bacillus spp*, two by *B. cereus*, and one by *B. licheniformis*. All three patients had hematologic neoplasia and implantable port, where two patients underwent catheter removal, and one patient required PICU management.

Table 4. Blood cultures isolated microorganisms and lock therapy treatment

Microorganism	n (%)	Lock therapy	Therapy success n (%)
Staphylococcus epidermidis	15 (20)	Vancomycin: 12 Ethanol: 2 Cefazolin: 1	8 (53)
Escherichia coli	9 (12)	Aminoglycoside: 9	8 (89)
Streptococcus mitis	8 (11)	Vancomycin: 5 Ethanol: 2 Ampicillin: 1	7 (88)
Klebsiella pneumoniae	7 (9)	Aminoglycoside: 7	5 (71)
Staphylococcus aureus	7 (9)	Cefazolin: 6 Ethanol: 1	6 (86)
Enterobacter cloacae	5 (7)	Aminoglycoside: 5	4 (80)
Staphylococcus hominis	5 (7)	Vancomycin: 5	3 (60)
Serratia marcescens	3 (4)	Aminoglycoside: 2 Ciprofloxacina: 1	2 (67)
Bacillus cereus y *Bacillus licheniformis*	3 (4)	Aminoglycoside: 1 Vancomycin: 1 Ampicillin: 1	1 (33)
Salmonella spp	2 (3)	Ciprofloxacina: 1 Ethanol: 1	2 (100)
Pantoea spp	2 (3)	Aminoglycoside: 2	2 (100)
Pseudomonas aeruginosa	1 (2)	Ethanol: 1	1 (100)
Others*	7 (9)	Aminoglycoside: 3 Ethanol: 2 Cefazolin: 1 Vancomycin: 1	5 (71)

*Others: *Brevundimonas diminuta, Haemophilus influenzae, Streptococcus pyogenes, Streptococcus salivarius, Streptococcus sanguis, Enterococcus faecalis, Enterobacter asburiae* cada uno en un paciente.

Prophylactic therapeutic lock

In prophylaxis, therapeutic lock with 70% ethanol was used in all episodes (13) in 7 patients, all with chronic gastrointestinal pathology, with a predominance of patients with intestinal failure. The median age of these patients was 7 months (IQR 5-12 months), with a predominance of male sex (71%) (table 1). These patients, due to their condition, all had a Broviac catheter that was implanted by interventional radiology. The most frequent catheter insertion site was thoracic (6 patients), followed by jugular (5 patients), and hypochondrium (2 patients). Catheter preservation was achieved in 8 cases (62%). The median number of infection-free days with prophylactic therapy was 29 days (IQR 6.5 - 35 days). Of the patients who presented CRBSI, one required admission to the PICU. No patient with this therapy died, nor was there any damage to the CVC that required its removal for this reason.

Discussion

This is one of the largest series reported so far in Latin America, which included 67 episodes in 54 patients with CVC and therapeutic lock for CRBSI treatment, achieving catheter preservation in 75% of patients, with aminoglycosides being the most frequently used antibiotics (38%). In addition, we report a description of 13 episodes in 7 patients with prophylactic therapeutic lock with 70% ethanol, where the catheter was preserved in 62%, all with chronic gastrointestinal pathology.

Therapeutic lock

The studies on therapeutic lock are very variable, including differences in design, and inclusion criteria, some only evaluate patients with cancer, others only with intestinal failure, and others include a wide range of diagnoses. Additionally, other studies only evaluate ethanol therapy and others include antibiotics in therapeutic lock.

The median age in this study was 4 years, different from that found in other series of cancer patients where the average age varies between 6.5 and 8.3 years[7,8], probably because our study includes other patients such as children with intestinal failure and esophageal atresia, pathologies that occur at an earlier age. The sex in some studies is predominantly female[7], while in others is male[8,9], as occurred in our study. In a Japanese population that received ethanol therapeutic lock, children older than 1 year were included, with a median age of 9.4 years, and were predominantly male[10].

The main diagnosis in this series was hematological neoplasms contrary to what was found in other studies where solid tumors predominated[7,11], but similar to what was reported in other series where only patients with cancer were included[8,12] which may be explained by the nature of our institution, which is a national reference center and of high complexity. In a similar Australian institution, malignant pathologies were more frequently followed by intestinal failure, similar to our results[9].

To our knowledge, there is only one other series in Latin America that included 11 episodes in 8 patients with cancer and antibiotic therapeutic lock, in which a high rate of central catheter preservation was obtained[13], similar to our results in the same population.

Therapeutic lock with antibiotics or ethanol has been shown to achieve high catheter preservation (84-85%)[7,10], both in oncologic patients and in patients with intestinal failure and other pathologies, data similar to our results (75%). In cancer patients, in this series, catheter preservation was achieved in 80% of the cases, including during the time of febrile neutropenia, which was present in 88% of these patients. These data contrast with those reported in the systematic review and meta-analysis of the Cochrane Collaboration (2013), where no differences were found in the addition of parenteral antibiotics, therapeutic lock with ethanol or urokinase in cancer patients; however, the sample size was very small, and the follow-up was short[6]. The most recent meta-analysis by Lai et al. included 5 studies (n = 2294), 3 of these in neonates, one in PICU patients with multiple pathologies, and another with patients in postoperative cardiovascular surgery, in which no evidence was found of the benefit of antibiotic therapeutic lock, for which reason they call on the scientific community to carry out high-quality studies on this subject[14]. Similarly, the consensus of the Latin American Society of Pediatric Infectious Diseases on the management of episodes of febrile neutropenia in children with cancer, considers that there is not enough evidence available to routinely recommend therapeutic lock, but leaves it to the consideration of each center according to its experience and epidemiology for cases of recurrent bacteremia and difficult vascular access[15].

The Infectious Diseases Society of America (IDSA) guidelines indicate antibiotic therapeutic lock for bacteremia associated with uncomplicated long-term CVC (without insertion site or tunnel infections or osteomyelitis or endovascular infection), associated with parenteral antibiotics to preserve the catheter. Exceptions to this are infections by *S. aureus*, *P. aeruginosa*, *Bacillus spp*, *Micrococcus spp*, cutibacterium species, or *Candida spp*[2]. In this series, 15% of the patients received therapeutic lock with isolation of one of these microorganisms (*S. aureus*, *P. aeruginosa*, and *Bacillus spp*), with success in 72% of the cases. This was because

the patients had no other vascular access option. This practice is not so infrequent, for example, Mandolfo et al. published in 2019 a case series of hemodialysis patients with CRBSI due to *S. aureus*, who received therapeutic lock, with a success rate of 85% (34 of 40 episodes), however, relapses occurred in 24% (6 of 34) and treatment of bacteremia lasted 4 weeks[16].

In a study with therapeutic lock with meropenem in neonates, it was reported that 4 catheters were preserved in patients with *Klebsiella pneumoniae* infection[17]. This antibiotic is not contemplated in the protocol of our institution for use in therapeutic lock since it is performed with amikacin with acceptable success. In our study, no patient who presented fungal infection received therapeutic lock, different from other series[7,10,17]. Protocols from other institutions include other solutions (Ceftazidime, daptomycin, and 50% ethanol) or antifungals (amphotericin B) in therapeutic lock[18,19], different from our protocol.

Unlike other studies, in our protocol, therapeutic lock is not administered to PICC[20]. Polymicrobial isolation was similar to the results of other series[7,10], although other studies did not perform therapeutic lock under these conditions[20]. The duration of therapeutic lock is recommended for 10 to 14 days[2], finding that our results follow this recommendation and the institutional protocol.

Prophylactic therapeutic lock

Regarding prophylactic therapeutic lock, few studies evaluate it in patients with long-term catheters. The IDSA guideline does not recommend treatment for CRBSI with ethanol given the little evidence available at the date of publication, however, there are increasingly more publications reporting good results, with catheter preservation data from 77 to 100% of cases, including the 2016 GAVeCeLT consensus[4,10,11,21-23].

In this series, we found that ethanol prophylaxis preserved the catheter in 62% of patients with intestinal failure, similar to that reported in the meta-analysis by Rahhal et al. in patients with intestinal failure and TPN, where ethanol therapeutic lock decreased CRBSI and catheter replacement[23]. In a cancer population, Wolf et al. found no differences with prophylactic ethanol therapy to prevent CRBSI; on the contrary, there were more catheter occlusions[12]. In our institution, prophylactic antibiotic therapy is not used so far, according to the most recent guidelines[4], unlike what has been described in other studies for hemodialysis catheters[24].

A network meta-analysis compared therapeutic lock solutions in pediatric patients with CRBSI, concluding that taurolidine appears to be more effective in preventing CRBSI than other solutions such as ethanol, fusidic acid, amikacin, or vancomycin[25]. Another recent study compared therapeutic lock with taurolidine and ethanol in patients with intestinal failure, finding that with taurolidine there were fewer ruptures, fewer occlusions, and catheter repairs, but the CRBSI and catheter replacement rates were similar[26]. To define the use of taurolidine in low- and middle-income countries such as ours, cost-effectiveness studies are necessary. In the cases described in this study, no serious catheter damage was reported with the use of 70% ethanol, which would have required catheter removal, although the sample size was small. Several adverse effects have been described with ethanol lock such as CVC occlusion due to thrombosis, catheter structural changes, and systemic toxicity[27], however, in a more recent meta-analysis comparing ethanol lock and heparin controls, no differences were found in dysfunction, withdrawal, CVC thrombosis, and mortality[28].

Although the most commonly used antiseptic solution in our milieu is 70% ethanol[23], there is a pilot study by Calderon and Rahhal with the use of 30% ethanol in 6 patients with intestinal failure and found that this therapy could be effective in preventing CRBSI[29]. Also, other solutions have been studied for this purpose, with more evidence in this regard for hemodialysis catheters[30].

The main limitation of this study was that it was performed in a reference center, which may represent selection bias due to the complexity of the patients and a small sample size in patients with prophylactic therapy.

In conclusion, in this series, we found that the catheter was preserved in 75% of cases when therapeutic lock was used, with a high percentage in oncologic patients (80%) and with neutropenia (88%). Aminoglycosides, vancomycin, and 70% ethanol were the most commonly used drugs in this therapy. Mortality associated with CRBSI was 6% and admission to PICU occurred in 25%. 15% of patients received therapeutic lock for *S. aureus*, *P. aeruginosa*, and *Bacillus spp* infection, with success in 72% of cases.

With prophylactic therapeutic lock with 70% ethanol, the catheter was preserved in 62%, all patients had chronic gastrointestinal pathology and Broviac catheter. The median number of infection-free days was 29 days.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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