Ethanol Lock Therapy (E-Lock) in the Prevention of Catheter-Related Bloodstream Infections (CR-BSI) after Major Heart Surgery (MHS): A Randomized Clinical Trial

María Jesús Pérez-Granda1,5,6*, José María Barrio1,5,6, Patricia Muñoz2,4,5,6*, Javier Hortal1,5,6, Cristina Rincón1, Pablo Martín Rabadán2,4,5,6, María Sagrario Pernia3, Emilio Bouza2,4,5,6

1 Department of Anesthesiology, School of Medicine, Universidad Complutense, Madrid, Spain, 2 Department of Clinical Microbiology and Infectious Diseases, School of Medicine, Universidad Complutense, Madrid, Spain, 3 Department of Pharmacy, Hospital General Universitario Gregorio Marañón, Madrid, Spain, 4 Medicine Department, School of Medicine, Universidad Complutense, Madrid, Spain, 5 Instituto de Investigación Biomédica Gregorio Marañón, Madrid, Spain, 6 CIBER Enfermedades Respiratorias-CIBERES (CB06/06/0058), Madrid, Spain

Abstract

Background: Lock-therapy with antimicrobials has been used for the treatment and prevention of catheter-related bloodstream infections (CR-BSI). Experiences with Ethanol-Locks (E-locks) have included therapeutic interventions with variable results. Patients undergoing Major Heart Surgery (MHS) are a high-risk population for CR-BSI. The aim of this study was to assess the efficacy and tolerance to E-Locks in the prevention of CR-BSI of patients undergoing MHS.

Methods and Findings: This is an academic, prospective, randomized, non-blinded and controlled clinical trial assessing the incidence of CR-BSI of patients with E-locks (E-lock) and the tolerance to the procedure in comparison with patients receiving conventional catheter-care (CCC). Patients undergoing MHS with intravascular catheters for more than 48 hours were randomly assigned into treatment or control group by a computer-generated list of randomly assigned numbers. In the treatment group, all their catheter lumens were locked with an ethanol solution at 70% for two hours, every three days (E-locks). The control group received conventional catheter-care (CCC). Overall, 200 patients with 323 catheters were included in the study, which was stopped after 10 months due to adverse events. Of them, 179 catheters (113 patients) had E-locks and 144 catheters (87 patients) were CCC. Euroscore Surgical Risk in both groups was 4.04 vs 4.07 p = 0.94 respectively. The results for the E-locks and CCC were as follows: Incidence of CR-BSI/1000 days of exposure 2.1 vs 5.2 (p = 0.33), catheter tip colonization 14 (7.8%) vs 6 (4.2%) patients (p = 0.17), median length of hospital stay, 15 vs 16 days respectively. The results for the E-locks and CCC were as follows: Incidence of CR-BSI/1000 days of exposure 2.1 vs 5.2 (p = 0.33), catheter tip colonization 14 (7.8%) vs 6 (4.2%) patients (p = 0.17), median length of hospital stay, 15 vs 16 days respectively. Seven patients (6.19%), all in the ethanol branch, had to discontinue the trial due to intolerance or adverse events.

Conclusions: We do not recommend prophylaxis of CR-BSI with ethanol-lock on a routine basis in patients undergoing Major Heart Surgery.

Trial Registration: Clinical Trials.gov NCT01229592

Citation: Pérez-Granda MJ, Barrio JM, Muñoz P, Hortal J, Rincón C, et al. (2014) Ethanol Lock Therapy (E-Lock) in the Prevention of Catheter-Related Bloodstream Infections (CR-BSI) after Major Heart Surgery (MHS): A Randomized Clinical Trial. PLoS ONE 9(3): e91838. doi:10.1371/journal.pone.0091838

Editor: Vineet Gupta, University of Pittsburgh Medical Center, United States of America

Copyright: © 2014 P Pérez-Granda et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This study was partially supported by a grant from Fondo de Investigacion Sanitaria, FIS EC07/90653 (Instituto de Salud Carlos III) and by the Rafael del Pino Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: massus@hotmail.es (MJPG); pmunoz@micro.hggm.es

Introduction

Patients undergoing Major Heart Surgery (MHS) are at a high risk of developing Catheter-Related Bloodstream Infections (CR-BSI), leading to a subsequent increase in morbidity and mortality [1–4].

Efforts developed to eliminate CR-BSI in patients hospitalized in Intensive Care Units (ICU’s) have mainly concentrated on mixed ICU’s and not specifically on patients following MHS, who usually require more catheters during more prolonged periods of time [5–7]. The programs addressed to eliminate CR-BSI episodes are mainly based on educational policies and on non-pharmacological measures and, although effective, these programs fail to lead to the disappearance of CR-BSI in most units and are often difficult to maintain for prolonged periods of time [8,9].

The use of antibiotic lock solutions to treat CR-BSI has been relatively successful in specific situations, such as pediatric patients or home total parenteral nutrition related infections [10–12]. However, there is a concern about the potential risk of those solutions to induce the development of antibiotic therapeutic resistance [13]. Ethanol locks (E-locks) were greeted as a potential non-antibiotic alternative for the rescue of infected long-term catheters that were very difficult to substitute in different and disparate populations [14–18]. E-locks, however, have not been evaluated as a systematic procedure for the prevention of CR-BSI in the short-term use of catheters.
Our study is a prospective, randomized trial, evaluating the efficacy and tolerance to E-locks in the prevention of CR-BSI and catheter colonization in patients admitted to a specific MHS-ICU.

**Materials and Methods**

Our institution is a general reference hospital with 1,550 beds and approximately 55,000 admissions/year during the study period. The Department of Cardiovascular Surgery is a large referral Unit that performs more than 500 MHS procedures annually. The start date of participant recruitment was February, 2011.

**Study Design**

Our study is a prospective, randomized, academic clinical trial, not funded by pharmaceutical or biotechnology companies. The patient inclusion criteria were:

- Recent MHS admission with Central Vascular Catheters (CVC) inserted >48 hours.
- Age >18 years.
- No evidence or suspicion of CR-BSI at enrolment: No signs of infection neither general nor at catheter site entrance.
- No history of allergy or intolerance to ethanol or chronic liver disease.
- No pregnancy.

Patients who gave their informed consent were randomly assigned into two groups: Ethanol group (E-lock) and conventional catheter-care (CCC). Patients assigned to E-locks had CCC plus all catheter lumens locked with 1 mL of an ethanol solution at 70% for a period of 2 hours every three days, until catheter withdrawal. After the two hours, the ethanol was flushed through with 1 mL of saline solution.

Both groups received CCC according to standard recommendations and all catheters had split-septum connectors [19]. All catheters were withdrawn when clinically required and the catheter tips were systematically sent for culture.

**Preparation of the ethanol solution**

The 70% ethanol solution was prepared by the Pharmacy Department as a sterile solution and was produced in 5 mL single dose vials after approval by the Spanish Agency for Medicines and Health Products and as established by the Spanish Legislation (Real Decreto 223/2004-Spain).

**Endpoints of the Study**

The primary endpoint was the incidence of CR-BSI during the admission for Surgery.

**Secondary endpoints were**

1. - The rate of colonization of the skin surrounding the catheter entrance, the hubs and the catheter tips in the E-lock and the CCC group.
2. - Antibiotic consumption in the two groups.
3. - Hospital stay, ICU stay and mortality in both groups of patients.
4. - Tolerance to the ethanol locks.

**Ethics**

The protocol for this trial and the CONSORT checklist are available as supporting information, see Checklist S1 and Protocol S1. The Ethics Committee of our institution (Hospital General Universitario Gregorio Marañón) approved the study and all patients gave their written informed consent before inclusion in the study.

**Follow-up of patients**

Patients were followed-up daily to check for the presence of infections and adverse reactions by both the physicians of the Department of Anaesthesia and by Infectious Disease specialists participating in the study. Clinical data were recorded according to a pre-established protocol and no further systematic surveillance cultures were performed.

**Pre-surgical information**

Included epidemiological data, underlying diseases and standard scores (ASA, EuroSCORE, Charlson comorbidity index and APACHE II score on admission to the ICU).

**Surgical information**

Included type of surgery, indication, duration, time of cardiopulmonary by-pass, aortic cross-clamp time and antimicrobial prophylaxis. Antimicrobial prophylaxis for surgery consisted of 2 g of cefazolin given before surgery and every 8 hours thereafter for a total of 3 doses (patients who were allergic to cefazolin received 1 g vancomycin before surgery).

**Postsurgical outcome**

Enrolled patients were prospectively followed for the occurrence of CR-BSI until catheter withdrawal, hospital discharge or death. Outcome variables also included antimicrobial use measured as daily defined doses (DDD’s), *Clostridium difficile* infection (CDI) episodes, length of ICU stay, ICU mortality, length of hospital stay and mortality at discharge.

- For each intravascular line, the following data were recorded: type of catheter, insertion site, cause of removal, result of tip, skin and hub cultures and presence or absence of CR-BSI. Catheters were made of polyurethane and were non antibiotic coated.

**Data regarding adverse events**

The following data were systematically collected in both populations after the ethanol or conventional locks were flushed: subjective tolerance, catheter obstruction, elevation of liver function enzymes and reasons for catheter withdrawal.

**Definitions**

The definitions of CR-BSI are those detailed in the recent Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection [19]. For the purpose of this study we only accepted microbiologically proven CR-BSI considered when the same microorganism was recovered from blood and a catheter tip within less than 8 days. Catheter tip colonization, hub and skin colonization are defined as the presence of ≥15 colony forming units in the semiquantitative culture according to the roll plate technique recommendation [20].

**Statistical analysis**

Considering that the previous incidence density of CR-BSI in our unit was 3.7 episodes/1000 catheter-days before the study, in order to be able to detect a difference of 25% between the two groups with 80% power and a 5% level of significance, we estimated that the sample size for the whole study should be 950 patients, divided equally in 475 in each arm.

Relationships between baseline variables were evaluated for the randomized groups. Basal comparisons between groups were
established by clinical relevance according to the CONSORT recommendations [21]. The qualitative variables appear with their frequency distribution. The quantitative variables were reported as the mean and standard deviation (SD) and as the median and inter-quartile range (IQR) if their distribution was skewed. Continuous variables were compared using the Student’s t test for normally distributed variables or median test for non-normally distributed variables. The Chi 2 or Fisher’s exact test was used to compare categorical variables. The Kolmogorov-Smirnov test was used to check whether a variable had a normal distribution.

Multivariate analysis. CR-BSI incidence rates (event/1000 days of CVC) between E-lock and CCC group were compared by Cox regression including all the variables statistically or clinically associated with treatment in the univariate analysis. HR (hazard ratio) and 95% CI were also calculated. All statistical tests were two-tailed. The level of significance was set at p<0.05 for all the tests. The statistical analysis was performed with SPSS 12.0 and Stata 9.0 software.

Results

The study was terminated early due to side effects. During the study period (February 28, 2011 to December 31, 2011), 408 patients underwent MHS. Of them, 234 gave their informed consent to participate in the study. From these cases, 34 had to be excluded due to different reasons, including patients without CVC at the time of inclusion, death during surgery, early postoperative deaths, suspicion of infection immediately before the lock administration, or consent withdraw. The remaining 200 patients constitute the Intention to Treat Population (ITT) and 198 the Per-Protocol Population (PP). Only 2 patients failed to receive at least 1 dose of ethanol lock. The statistical analysis performed in both populations (ITT and PP) rendered similar results. The results of the ITT cohort are the ones shown in the manuscript.

The patients in the study were randomized to the E-lock (113 patients) or CCC (87 patients) (Figure 1).

Basal (Pre-Surgery) information in both populations

The characteristics of both populations and their co-morbidities are compared in Table 1. Sex, co-morbidities, underlying conditions, APACHE II score, ASA score and EuroSCORE (4.04 ± 2.5 in the E-lock group vs 4.07 ± 2.5 in the CCC group: p = 0.94) were similar in both groups of patients. The APACHE II score was respectively 8.89 (± 2.7) for the E-lock and 8.86 (± 2.5) for the Control Group, with no significant differences between them.

Data of the surgical procedure

Type of surgery, mean time on cardiopulmonary by-pass, aortic cross-clamp time and antimicrobial prophylaxis were similar in both groups (Table 1).

Vascular access

Both populations showed no significant differences in the total number of catheters, mean number of catheters per patient, location of catheters, days of exposure to catheters, use of lipid or parenteral nutrition and other parameters (Table 2).

Lock procedures

The lumens of catheters in the ethanol group were locked sequentially every 3 days with 1 ml of 70% ethanol solution. After the 2 hour locks, the lumens were flushed with 5 ml of normal saline.

The total number of locks (all catheters lumens) that were made with ethanol was 338, with a range that varied between 1 and 25 locks per patient (median 2.0). Dwell time was 2 hours, uniformly in all cases.

Primary endpoints

Post-surgical outcomes of both populations are summarized in Table 3. The number of episodes of CR-BSI was 2 episodes in the ethanol group (2.1 episodes/1,000 days of exposure) and 4 episodes in the control group (5.0 episodes/1000 days of exposure). The calculated incidence rate ratio was 0.42 (95% confidence interval 0.04–2.90), which implies a non-significant reduction of 58% for patients treated with ethanol locks (p = 0.33). The episodes of CR-BSI occurred in days 4 to 44 postoperatively and the etiology of the episodes is shown in Table 3.

Secondary endpoints

We were not able to demonstrate differences in the secondary endpoints of the study (Table 3), including days in the ICU and hospital stay, days of catheter exposure and number of colonized catheters. No differences were detected between both groups in the incidence of other infections, antibiotics consumption, incidence of CDI, ICU or hospital mortality (Table 3).

Adverse events

The adverse events of both groups are summarized in Table 4. Obstruction of catheters that required catheter withdrawal occurred in 3 patients in the ethanol group and in 4 patients in the control group (p = 0.87) (Table 4). In 7 patients the ethanol locks could not be completed, in five of them due to hemodynamic instability (high doses of inotropics). One catheter in the ethanol group had to be removed because of the rupture of 1 of the 3 lumens (Table 4).
In the five minutes following the flushing of the lock solutions, 2 patients in the ethanol group presented important adverse events. One had chest pain accompanied by high blood pressure, without any other hemodynamic or electrocardiographic changes. The chest pain disappeared rapidly after the catheter was withdrawn. The second patient developed intense headaches and photopsies. The flushing was stopped and the catheter withdrawn. The catheter tip from this patient was inappropriately placed in the upper jugular vein. The comparison of liver enzymes, ALAT and ASAT was not significantly different between both groups (Table 4).

Microorganisms isolated from colonization and CR-BSI episodes

For the purpose of this study, all removed catheters were sent for culture to the Microbiology Department (314 of 323). Overall, 20 patients showed a positive semiquantitative count of the catheter tip. Of these, 14 belonged to the E-lock group, while 6 were in the CCC group (p = 0.17).

Surveillance cultures of the peri-catheter skin and hubs were systematically done until catheter removal. The number of patients with one or more positive surveillance cultures was not significantly different in the population treated with ethanol (31/113) than in the conventional treatment population (26/87) (p = 0.70).

The microorganisms present in significant counts in surveillance cultures are summarized in Table 5. No significant differences were found in the microorganisms causing CR-BRSI or colonization in both groups.

Multivariate analysis

In the multivariate analysis the difference of the incidence density of CR-BSI, between the E-lock and CCC groups was not significant. The number of patients needed to be treated with ethanol-locks to prevent one CR-BSI episode was 345.

Discussion

Our study shows that despite a trend in the reduction of CR-BSI, the use of ethanol locks for the prevention of CR-BSI in patients undergoing MHS should not be recommended. It is cumbersome and associated with serious adverse events.

In recent years, different campaigns have emphasized the need to drastically reduce CR-BSI and have set zero tolerance concept to those infections [8,22]. Achieving and maintaining the zero incidence, however, proved to be a very difficult or impossible task, even in situations and institutions that made very serious and obstinate efforts [23,24]. The search for alternative, non-educational procedures to contribute to a zero incidence remains pertinent, particularly in populations with many catheters and at a
Table 2. Characteristics of Vascular Access in both groups.

|                                | Ethanol N = 113 | Control N = 87 | p value |
|--------------------------------|-----------------|---------------|---------|
| Total catheters (n)            | 179             | 144           | 0.44    |
| Cultures taken (n)             | 1289            | 1147          | 0.37    |
| Patients with Positive cultures| 31              | 26            | 0.70    |
| Total Catheter exposure (days)  | 955             | 805           | —       |
| Days of catheter exposure. Median (IQR) | 6 (4–8) | 7 (5–9) | 0.55 |
| Type of catheter (%):          |                 |               | 0.58    |
| Conventional                   | 122 (68.2%)     | 94 (65.3)     |         |
| Swan-Ganz                      | 57 (31.8)       | 50 (34.7)     |         |
| Location (%):                  |                 |               | 0.34    |
| Jugular                        | 172 (96.1)      | 141 (97.9)    |         |
| Subclavian                      | 7 (3.4)         | 3 (2.1)       |         |
| Total Parenteral Nutrition (%) | 6 (3.4)         | 6 (4.2)       | 0.70    |
| Reasons for catheter withdrawal (%): |             |               | 0.85    |
| End of use                     | 166 (92.8)      | 135 (93.8)    |         |
| Obstruction                    | 5 (2.8)         | 4 (2.8)       |         |
| Suspicion of infection         | 3 (1.7)         | 3 (2.1)       |         |
| Adverse events                 | 2 (1.1)         | 0             |         |

doi:10.1371/journal.pone.0091838.t002

Table 3. Clinical outcome in all randomized patients

|                                         | Ethanol N = 113 | Control N = 87 | p value |
|-----------------------------------------|-----------------|---------------|---------|
| Catheter colonization:                  |                 |               |         |
| Overall (%)                             | 39 (21.8%)      | 36 (25%)      | 0.32    |
| Skin (%)                                | 30 (16.8)       | 32 (22.2)     | 0.21    |
| Skin colonization (density/1000 catheter-days) | 39.52       | 49.53         | 0.38    |
| Hub (%)                                 | 4 (2.2)         | 3 (2.1)       | 0.92    |
| Hub colonization (density/1000 catheter-days) | 4.40          | 3.82          | 0.87    |
| Tip colonization (%)                     | 14 (7.8)        | 6 (4.2)       | 0.17    |
| Tip colonization (density/1000 catheter-days) | 15.26         | 8.0           | 0.19    |
| CR-BSI: Episodes (%)                     | 2 (1.8)         | 4 (4.6)       | 0.24    |
| CR-BSI Density per 1000 catheter-days   | 2.17            | 5.24          | 0.33    |
| Other infections (%):                   |                 |               |         |
| Urinary tract infection                 | 7 (6.2)         | 7 (8.0)       | 0.61    |
| Bacteremia                              | 6 (5.5)         | 6 (7.1)       | 0.64    |
| Ventilator associated pneumonia         | 2 (1.8)         | 3 (3.4)       | 0.45    |
| Surgical Wound Infection               | 3 (2.7)         | 0 (0)         | 0.12    |
| Clostridium difficile-infection         | 2 (1.8)         | 1 (1.1)       | 0.63    |
| Days of Stay Median (IQR):              |                 |               |         |
| ICU                                      | 5 (3–7)         | 6 (3–7)       | 0.75    |
| Hospital                                | 15 (12–25)      | 16 (13–28)    | 0.77    |
| Mortality in hospital (%)               | 7 (6.2)         | 7 (8.0)       | 0.61    |
| Overall DDD's of AA during hospital stay. Mean (SD) | 7.99 (18.6) | 9.11 (16.5) | 0.65    |

Abbreviations: IQR: interquartile range; DDDs: daily defined doses; AA: Antimicrobial Agents.
doi:10.1371/journal.pone.0091838.t003
high risk for CR-BSI, as it is the case of patients undergoing MHS [25].

The use of high concentrations of antibiotics in the catheter lumens (lock-therapy) proved to be effective both in the conservative treatment management of infected catheters [11,26] and also as a prophylactic approach in certain situations [27,28]. Antibiotics, however, have different activities against different microorganisms, their penetration in the catheter biofilm is highly variable and the long-term use of antibiotic-locks, mainly in prophylaxis, may lead to the development of antimicrobial resistance [13,29].

Ethanol is easy to produce and has a broad spectrum of antimicrobial activity, including bacteria and *Candida* [28,30–32]. Studies of ethanol lock as a therapeutic agent for the treatment of CR-BSI are frequently based on case reports or very short series [33] and usually selected for treatment of episodes caused by “easy to treat” microorganisms such as Coagulase Negative Staphylococcus. Under these circumstances, eradication of infections were obtained in up to 86% of the episodes in the McGrath’s study [17]. The tolerance to alcohol in those studies was generally good [33,34] but thrombosis and other adverse events were reported [15,35].

Data regarding the efficacy of ethanol locks in the prevention of CR-BSI is scarce. A meta-analysis in pediatric patients with short bowel syndrome and long-term catheters carried out by Oliveira et al [16], found 4 retrospective studies in this population. In comparison with heparin-locks, ethanol locks reduced the CR-BSI-rate by 81% and the need of catheter replacements by 72%. Overall, 108 to 150 catheter days of ethanol exposure were necessary to prevent one CR-BSI episode and 122 to 689 days of exposure prevented one catheter replacement.

In the case of hematologic patients with tunneled catheters, a randomized, double-blind, placebo-controlled trial compared ethanol locks for 15 minutes per day with a placebo. No significant differences were found between both groups in the incidence of CR-BSI, but more patients receiving ethanol discontinued lock-therapy (11 of 226 versus 1 of 222; p = 0.006) or continued with decreased lock-frequency (10 of 226 versus 0 of 222; p = 0.002) due to non-severe adverse events. In patients allocated to ethanol locks, one device had to be removed because of the rupture of 1 of the 3 catheter lumens. Facial flushing occurred in 39 out of the 226 patients with ethanol, compared to 17 out of the 222 patients with placebo (p < 0.001) and feelings of dizziness/drowsiness occurred in 41 and 10 patients with ethanol or placebo respectively (p < 0.001) [36].

Occasional information indirectly suggest the effectiveness of ethanol in preventing infections in the subgroups of patients on Total Parenteral Nutrition [15,34] and in other patients [37] but different adverse events including thrombosis and catheter dysfunction were also reported [15,35,38].

Our population, of patients undergoing Major Heart Surgery, is a uniform but different population, frequently hemodynamically unstable and with highly needed central lines. The number of CR-BSI was reduced by 58% in patients receiving ethanol in our study, but the differences did not reach statistical significance, probably due to the early stop of our study and the consequent low power. Our calculations show that to prevent an episode of CR-BSI in our patients, 345 cases would have to receive prophylactic ethanol.

| Table 4. Adverse events. |
|-------------------------|
| Ethanol N = 113 | Control N = 87 | p value |
| Discontinuation of the study compound | 7 | 0 | 0.018 |
| Severe immediate adverse events | 2 | 0 | 0.21 |
| Rupture of the catheter lumen | 1 | 0 | 0.37 |
| Patients with ALAT–ASAT elevations (double than normal value) | 42 | 33 | 0.91 |

**Table 5. Microorganisms present in significant counts in surveillance cultures and CR-BSI.**

| CR-BSI (6): | Ethanol N = 113 | Control N = 87 | p-value |
|------------|----------------|----------------|---------|
| Gram positive cocci (%) | 2 | 4 | 0.82 |
| *Enterobacteriaceae* (%) | 0 | 1 (1.14) |
| GNNFR (%) | 2 (1.76) | 2 (2.29) |
| Fungi (%) | 1 (1.14) |
| Colonized patients (57) (1 species per patient): | 0.83 |
| Gram positive cocci (%) | 35 (30.97) | 27 (31.03) |
| *Enterobacteriaceae* (%) | 4 (3.53) | 2 (2.29) |
| GNNFR (%) | 0 | 1 (1.14) |
| Fungi (%) | 1 (0.88) | 1 (1.14) |

GNNFR: Gram negative non-fermenting rods.
We selected as a primary end-point CR-BSI instead of CLABSI (Central Line Associated Bloodstream Infection). CLABSI is an approximate concept useful for epidemiological surveillance, while CR-BSI requires the confirmation with catheter cultures of the etiology and origin of CR-BSI. In our study the culture of catheter tip was only performed upon in-hospital withdrawal of catheters. To avoid this problem, we had to stop the trial after 10 months and our study was necessarily be extrapolated to other populations. Also very importantly, due to the detection of adverse events in the ethanol branch, we had to stop the trial after 10 months and our study was underpowered to detect a significant reduction of the CR-BSI episodes.

The limited and doubtful reduction of CR-BSI with the use of ethanol locks, the adverse events, the workload of the procedure for the nursing staff, the need for a high frequency of catheter manipulation and the requirement to lock highly needed lines during 2 hours, were among the reasons to stop our study. We do not recommend further studies with ethanol lock in the prevention of CR-BSI in patients following MHS.

Acknowledgments

We thank Laurence Baron for his help in the preparation of the English version of the manuscript and Cristina Fernández for the statistical analysis.

Author Contributions

Conceived and designed the experiments: MJPG EB. Performed the experiments: MJPG JMB PM JH CR PMR MSP EB. Analyzed the data: MJPG JMB PM EB. Contributed reagents/materials/analysis tools: PMR MSP. Wrote the paper: MJPG PM EB. Approved the manuscript: MJPG JMB PM JH CR PMR MSP EB.

References

1. Kohli M, Sharpless L, Vlasak J, Pasque C, Murphy D, et al. (1997) The impact of nosocomial infections on patient outcomes following cardiac surgery. Chest 112: 666–675.
2. Rebollo MH, Bernal JM, Lórea J, Rabasa JM, Revuelta JM (1996) Nosocomial infections in patients having cardiovascular operations: a multivariate analysis of risk factors. J Thorac Cardiovasc Surg 112: 908–913.
3. Le Guillou V, Tavolacci MP, Baste JM, Hubscher C, Bedoet E, et al. (2011) Surgical site infection after central venous catheter-related infection in cardiac surgery. Analysis of a cohort of 7557 patients. J Hosp Infect 78: 236–241.
4. Bouza E, San Juan R, Munoz P, Pascas J, Voss A, et al. (2004) A European perspective on intravascular catheter-related infections: report on the microbiology workload, aetiology and antimicrobial susceptibility (ESGN1-005 Study). Clin Microbiol Infect 10: 830–842.
5. Zack J (2000) Zeroing in on zero tolerance for central line-associated bacteremia. Am J Infect Control 36: S176 e171–172.
6. Kim JS, Holton P, Vigen C (2011) Reduction of catheter-related bloodstream infections through the use of a central venous line bundle: epidemiologic and economic consequences. Am J Infect Control 39: 640–646.
7. Bértés MG (2011) Prevention of catheter-related bloodstream infection in patients on hemodialysis. Nat Rev Nephrol 7: 257–265.
8. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, et al. (2006) An intensive care unit-based multifactorial intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 355: 2725–2732.
9. Palomar Martínez M, Alvarez Lerma F, Riera Badía MA, Leon Gil C, Lopez Puyó MJ, et al. (2010) [Prevention of bacteremia related with ICU catheters by multifactorial intervention: a report of the pilot study]. Med Intensiva 34: 501–509.
10. Opilla MT, Kirby DF, Edmond MB (2007) Use of ethanol lock therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients. J Parenter Enteral Nutr 31: 302–305.
11. Kim EY, Saunders P, Yousefzadeh N (2010) Usefulness of anti-infective lock solutions for catheter-related bloodstream infections. Mt Sinai J Med 77: 549–558.
12. Huang EY, Chen C, Abdullah F, Aspelund G, Barnhart DC, et al. (2011) Emergence of gentamicin-resistant bacteremia in hemodialysis patients. Haemophilia 15: 1267–1271.
13. Le Guillou V, Tavolacci MP, Baste JM, Hubscher C, Bedoet E, et al. (2011) Surgical site infection after central venous catheter-related infection in cardiac surgery. Analysis of a cohort of 7557 patients. J Hosp Infect 78: 236–241.
14. Bouza E, San Juan R, Munoz P, Pascas J, Voss A, et al. (2004) A European perspective on intravascular catheter-related infections: report on the microbiology workload, aetiology and antimicrobial susceptibility (ESGN1-005 Study). Clin Microbiol Infect 10: 830–842.
15. Zuck J (2000) Zeroing in on zero tolerance for central line-associated bacteremia. Am J Infect Control 36: S176 e171–172.
16. Kim JS, Holton P, Vigen C (2011) Reduction of catheter-related bloodstream infections through the use of a central venous line bundle: epidemiologic and economic consequences. Am J Infect Control 39: 640–646.
17. Giroletti EJ, Salloum R, Chen X, Jiang Y, Bolich-MacDonald K, et al. (2011) Short-dwell ethanol lock therapy in children is associated with increased clearance of central line-associated bloodstream infections. Clin Pediatr (Phila) 50: 943–951.
18. Broom J, Woods M, Althworth A, McCarthy J, Favaogli J, et al. (2006) Ethanol lock therapy to treat tunnelled central venous catheter-associated blood stream infections: results from a prospective trial. Scand J Infect Dis 40: 399–406.
19. O’Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, et al. (2011) Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control 39: S1–S35.
20. Maki DG, Weise CE, Sarafin HW (1977) A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med 296: 1305–1309.
21. Weller G, McNiel J (2010) CONSORT 2010 statement: updated guidelines can improve wound care. J Wound Care 19: 347–353.
22. Berenholtz SM, Pronovost PJ, Lipsert PA, Hobson D, Earsing K, et al. (2004) Eliminating catheter-related bloodstream infections in the intensive care unit. Crit Care Med 32: 2014–2020.
23. Palti H, Pati VC, Ramteerkar MN, Kulkarni RD (2011) Central venous catheter-related bloodstream infections in the intensive care unit. Indian J Crit Care Med 15: 213–223.
24. van der Koosi TI, Wille JC, van Beuthem BH (2012) Catheter application, insertion vein and length of ICU stay prior to insertion affect the risk of catheter-related bloodstream infection. J Hosp Infect 80: 238–244.
25. Bouza E, Munoz P, Burillo A, Lopez-Rodriguez J, Fernandez-Perez C, et al. (2005) The challenge of anticipating catheter tip colonization in major heart surgery patients in the intensive care unit: are surface cultures useful? Crit Care Med 33: 1953–1960.
26. Onder AM, Billings A, Chardar J, Franscoeur D, Simon N, et al. (2010) PREFABL: predictors of failure of antibiotic locks for the treatment of catheter-related bacteremia. Nephrol Dial Transplant 25: 3696–3699.
27. Yahav D, Rosen-Zvi B, Gafter-Gvili A, Lebovici I, Gafter U, et al. (2008) Antimicrobial lock solutions for the prevention of infections associated with intravascular catheters in patients undergoing hemodialysis: systematic review and meta-analysis of randomized, controlled trials. Clin Infect Dis 47: 83–93.
28. Ghanounou MA, Isham N, Jacobs MR (2011) Antimicrobial activity of B-Lock against bacterial and Candida spp. causing catheter-related bloodstream infections. Antimicrob Agents Chemother 55: 4430–4431.
29. Vendrus M, du Montcel SJ, Robert J, Tyszta D, Dighiero J, et al. (2010) Effect of catheter-lock solutions on catheter-related infection and inflammatory syndrome in hemodialysis patients: heparin versus citrate 46% versus heparin/gentamicin. Blood Purif 29: 268–273.
30. Shenep LE, Shenep MA, Cleatham W, Hoffman JM, Hale A, et al. (2011) Efficacy of intravascular catheter lock solutions containing preservatives in the prevention of microbial colonization. J Hosp Infect 79: 317–322.
31. Blackwood RA, Klein KG, Micell LN, Willers ML, Mody RJ, et al. (2011) Ethanol locks therapy for resolution of fungal catheter infections. Pediatr Infect Dis J 30: 1105–1107.
32. Raad I, Hanna H, Dvorak T, Chaiban G, Hachem R (2007) Optimal antimicrobial catheter lock solution, using different combinations of minocy-

Supporting Information

Checklist S1 CONSORT Checklist. (DOC)

Protocol S1 Trial Protocol. (DOC)

Protocol S2 Spanish Translation of Protocol S1. (DOC)
cline, EDTA, and 25-percent ethanol, rapidly eradicates organisms embedded in biofilm. Antimicrob Agents Chemother 51: 78–83.

33. Valentine KM (2011) Ethanol lock therapy for catheter-associated blood stream infections in a pediatric intensive care unit. Pediatr Crit Care Med 12: e292–296.

34. John BK, Khan MA, Speerhas R, Rhoda K, Hamilton C, et al. (2011) Ethanol Lock Therapy in Reducing Catheter-Related bloodstream infections in Adult Home Parenteral Nutrition Patients: Results of a Retrospective Study. JPEN J Parenter Enter Nutr.

35. Wong T, Clifford V, McCallum Z, Shalley H, Peterkin M, et al. (2011) Central Venous Catheter Thrombosis Associated With 70% Ethanol Locks in Pediatric Intestinal Failure Patients on Home Parenteral Nutrition: A Case Series. JPEN J Parenter Enter Nutr.

36. Slobbe L, Doorduijn JK, Lugtenburg PJ, El Barzouhi A, Boersma E, et al. (2010) Prevention of catheter-related bacteremia with a daily ethanol lock in patients with tunnelled catheters: a randomized, placebo-controlled trial. PLoS One 5: e10840.

37. Broom JK, Krishnasamy R, Hawley CM, Playford EG, Johnson DW (2012) A randomised controlled trial of Heparin versus EthAnol Lock THerapy for the prevention of Catheter Associated infecTion in Haemodialysis patients—the HEALTHY-CATH trial. BMC Nephrol 13: 146.

38. Heng AE, Abdelkader MH, Diaconita M, Nony A, Guerraoui A, et al. (2013) Impact of short term use of interdialytic 60% ethanol lock solution on tunnelled silicone catheter dysfunction. Clin Nephrol 75: 334–341.

39. Rodriguez-Creixems M, Munoz P, Martin-Rabadan P, Cerceno E, Guembe M, et al. (2013) Evolution and aetiological shift of catheter-related bloodstream infection in a whole institution: the microbiology department may act as a watchtower. Clin Microbiol Infect 19: 845–851.

40. McCabe W, Jackson GG (1962) Gram-negative bacteremia, I. etiology and ecology. Arch Inter Med 110: 847–55.

41. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40: 373–383.

42. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, et al. (1999) European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 16: 9–13.

33. Valentine KM (2011) Ethanol lock therapy for catheter-associated blood stream infections in a pediatric intensive care unit. Pediatr Crit Care Med 12: e292–296.