Clinical Microbiology and Infection 23 (2017) 86–91

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Procalcitonin to guide taking blood cultures in the intensive care unit; a cluster-randomized controlled trial

P.J. van der Geest [1,*], M. Mohseni [1], D. Nieboer [2], S. Duran [3], A.B.J. Groeneveld [1]

[1)] Department of Intensive Care Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands
[2)] Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands
[3)] Department of Intensive Care Medicine, Maasstad Hospital, Rotterdam, The Netherlands

ARTICLE INFO

Article history:
Received 18 June 2016
Received in revised form
2 October 2016
Accepted 3 October 2016
Available online 13 October 2016

Editor: L. Leibovici

Keywords:
Bacteraemia
Blood cultures
Critically ill
Efficacy
Procalcitonin
Safety

ABSTRACT

Objectives: We aimed to study the safety and efficacy of procalcitonin in guiding blood cultures taking in critically ill patients with suspected infection.
Methods: We performed a cluster-randomized, multi-centre, single-blinded, cross-over trial. Patients suspected of infection in whom taking blood for culture was indicated were included. The participating intensive care units were stratified and randomized by treatment regimen into a control group and a procalcitonin-guided group. All patients included in this trial followed the regimen that was allocated to the intensive care unit for that period. In both groups, blood was drawn at the same moment for a procalcitonin measurement and blood cultures. In the procalcitonin-guided group, blood cultures were sent to the department of medical microbiology when the procalcitonin was >0.25 ng/mL. The main outcome was safety, expressed as mortality at day 28 and day 90.
Results: The control group included 288 patients and the procalcitonin-guided group included 276 patients. The 28- and 90-day mortality rates in the procalcitonin-guided group were 29% (80/276) and 38% (105/276), respectively. The mortality rates in the control group were 32% (92/288) at day 28 and 40% (115/288) at day 90. The intention-to-treat analysis showed hazard ratios of 0.85 (95% CI 0.62–1.17) and 0.89 (95% CI 0.67–1.17) for 28-day and 90-day mortality, respectively. The results were deemed non-inferior because the upper limit of the 95% CI was below the margin of 1.20.
Conclusion: Applying procalcitonin to guide blood cultures in critically ill patients with suspected infection seems to be safe, but the benefits may be limited.
Trial registration: ClinicalTrials.gov identifier: ID NCT01847079. Registered on 24 April 2013, retrospectively registered. **P.J. van der Geest, CMI 2017;23:86**

Introduction

Critical illness predisposes to bacteraemia, thereby increasing morbidity and mortality [1,2], particularly when diagnosis and administration of antibiotics are delayed [3,4]. Indeed, culturing costs time, and only 15%–25% of blood cultures taken in critically ill patients suspected of infection prove positive, which suggests a waste of resources [5]. The use of biomarkers, including procalcitonin, has been studied to improve a fast and accurate diagnosis of sepsis and bacteraemia with varying results [4,6–8]. However, we recently performed a meta-analysis of studies suggesting that a normal procalcitonin has 96% negative predictive value for bacteraemia [9]. Based on nine studies, the area under the receiver operating characteristic curve of procalcitonin for bacteraemia in critically ill patients was 0.88 [6,9–17]. The studies included, however, were relatively small [10–12,15–17] and not primarily designed to rule out or detect bacteraemia [6,10,12–14]. Nevertheless, a rapidly available and normal procalcitonin might allow early prediction of negative blood cultures when blood sampling is clinically indicated for suspicion of infection, and might thereby avoid unnecessary blood culturing.

In the hypothesis that a normal procalcitonin can be used to predict absence of bacteraemia in critically ill patients, we aimed to

* Corresponding author. P.J. van der Geest, Department of Intensive Care Medicine, Erasmus Medical Centre, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands.
E-mail address: p.vandergeest@erasmusmc.nl (P.J. van der Geest).

http://dx.doi.org/10.1016/j.cmi.2016.10.004

study the usefulness of a rapidly determined procalcitonin, in saving blood cultures in critically ill patients in whom taking blood for culture is clinically indicated because of a suspicion of infection. We hypothesized that such a strategy can be safely applied in critically ill patients without increasing morbidity and mortality.

Materials and methods

Patients and study design

We performed a prospective, single-blinded, cluster-randomized, cross-over trial, involving the intensive care unit (ICU) of the Erasmus Medical Centre Rotterdam and the Maasstad hospital Rotterdam. We conducted this trial between January 2013 and September 2014. The ICU of the Erasmus Medical Centre is a tertiary-care mixed medical–surgery ICU with 2000 admissions per year. The ICU of the Maasstad Hospital is a secondary-care mixed medical–surgical ICU with 1200 annual admissions. The trial was conducted in accordance with the ethical principles decreed by the Declaration of Helsinki and in compliance with the International Conference on Harmonization of Good Clinical Practice Guidelines. The final protocol, amendments and informed consent document were reviewed and approved by the institutional review board (IRB) or the independent medical ethics committee at each of the investigational centres. This study was finally approved by the medical ethics committee of the Erasmus Medical Centre (MEC 2011-505) and registered with ClinicalTrial.gov (protocol ID NCT 01847079). We used the CONSORT guideline to construct our cluster-randomized trial (see Supplementary material, Tables S1 and S2). All patients or their proxy provided written informed consent before study inclusion, as a presumed consent at ICU admission.

Patients on the ICU $\geq$18 years in whom a suspicion of infection was raised and for whom taking blood for culture was clinically indicated by the attending intensivist were enrolled in the study. Suspicion of infection could be increasing body (tympanic) temperature >38.3°C, chills, progressive leucocytosis or increased C-reactive protein, increasing consolidations on chest radiography or other imaging of potential infection sources. Patients could be included more than once; every time that blood for culture is taken counts as a suspicion-of-infection episode (SIE). Patients were excluded if they had one of the following exclusion criteria: pregnancy, neutropenia (defined as leucocyte count $<0.5 \times 10^9$/L) and pre-terminal illness with an expected death within 24 hours. Patients were not included if blood cultures were performed as part of a standard protocol (such as patients with veno-venous or veno-arterial extracorporeal membrane oxygenation) or were performed to check the effectiveness of treatment (such as in endocarditis), unless the blood culture was performed because of an SIE. A flow chart of the included patients is given in the Supplementary material (Fig. S1). Patients were otherwise taken care of by board-certified intensivists, according to local and national guidelines. In case of a microbial infection source control was performed when possible and antibiotic treatments were given in close collaboration with a medical microbiologist.

Study protocol

The participating ICUs (two per medical centre) were stratified and randomized by treatment regimen into a control group (standard of care) and a procalcitonin-guided group. Randomization was performed per cluster allocation, being an assigned ICU. The stratified randomization and enrolment of patients was performed by one of the investigators. All patients included into this trial followed the regimen that was allocated to the ICU for that period. The participating units switched the allocated regimen every 3 months. We used a wash-out period between the cross-over period, to minimize the risk for a patient to follow two different regimens. The wash-out period was set for 1 month, in which >99% of the patients in the previous period have left the ICU. None of the patients included in this study followed two regimens. The participating ICUs were matched for a 1:1 ratio of allocation (see Supplementary material, Fig. S2). No changes to methods or trial outcomes have been made after trial commencement. The study was stopped after achieving at least 550 inclusions based on the power calculation.

In both the control and procalcitonin-guided groups blood was taken at the same moment for the procalcitonin measurement and blood cultures. In the control group, two sets of blood cultures were sent directly to the medical microbiology department. The procalcitonin measurement in the control group was determined by the department of clinical chemistry, and results were blinded for the investigators and only available before analysis. In the procalcitonin-guided group the procalcitonin measurement was determined as a stat determination, rendering results within 1 hour. Blood samples for the procalcitonin measurement were immediately centrifuged at 3000 rpm for 10 minutes at room temperature (Hettich Rotina 420R, Tuttlingen, Germany). The procalcitonin measurement was performed on the automated Kryptor platform (Brahms AG, Hennigsdorf, Germany), using the Roche Elecsys Brahms procalcitonin assay. Upon receiving results, the attending intensivists determined whether to send the blood cultures to the medical microbiology department. We used a cut-off of 0.25 ng/mL in the procalcitonin-guided group. Values below this cut-off were regarded as normal, and so not worth culturing (and blood cultures taken were destroyed). It was possible for the attending intensivists to overrule the procalcitonin-guided strategy and still send in blood cultures at normal procalcitonin. For values higher than the cut-off of 0.25 ng/mL, patients' blood cultures were sent to the medical microbiology department for further analysis. Each set of blood cultures consists of one aerobic and one anaerobic bottle (BD Bactec, Franklin Lakes, NJ, USA) containing resin to enhance the recovery of organisms. The blood cultures were incubated for 7 days in an automatic analyser (BD Bactec) that automatically demonstrates the time to positive blood culture in the case of positive bacterial or fungal growth. Gram strains were performed, and the organisms were cultured on agar plates and after growth identification was performed, using the VITEK® 2 (Biomérieux, Marcy l'Etoile, France) for bacteria and the Auxacolor (Sanofi Diagnostics Pasteur, Lyon, France) for fungal growth. The PCR technique was carried out using a LightCycler480 PCR system (Roche Diagnostics, Almere, the Netherlands) to detect viral growth in blood samples. Bacteraemia was defined as having a positive blood culture with a recognized pathogen except skin contaminants [18,19]. In the case of skin contaminants, bacteraemia was only considered if at least two blood cultures drawn on separate occasions were positive for the same microorganism [18,19]. We otherwise determined inflammatory parameters such as C-reactive protein (turbidimetric assay) and white blood cell counts (XN 9000, Sysmex, Kobe, Japan).

Data collection

At the day of inclusion, baseline demographic data and clinical variables, including age, sex, pre-morbidity, reasons of admission, use of antibiotics excluding selective decontamination of the digestive tract, antifungal treatment, steroids, immunosuppressive medication, immune status (active malignancy or other causes of an immunocompromised state), recent surgery, mechanical ventilation, renal replacement therapy, total parenteral nutrition, central