CRITIC

Pilot study

Coated devices to decRease InfecTion in the ICu

Statistical Analysis Plan

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SUMARRY

ABBREVIATIONS

AE	adverse event
ATB	antibiotics
CAUTI	catheter related urinary infection
CRBSI	catheter related bloodstream infection
CVC	central venous catheters
ICU	intensive care unit
ETT	endotracheal tubes
UC	urinary foley catheters
RR	risk ratio
SAP	statistical analysis plan
SOFA	sequential organ failure assessment
VAP	ventilator associated pneumonia

1. Administrative information

Statistical Analysis Plan (SAP) for the CRITIC Pilot Study (**C**oated devices to dec**R**ease **I**nfec**T**ion in the **IC**u).

- ClinicalTrials.org Registration: NCT03868241
- Protocol Version 2.0 – January, 2019.
- SAP Revision:

SAP version	Protocol Version	Descritption and Reason for Change	Date
1.0	2.0	Not Applicable	03/10/2019

2. Aim and objectives

The full rationale for undertaken the trial is explained in detail in the Protocol. Briefly, CRITIC is a pilot study to assess feasibility and potential recruitment rate for a larger trial using coated (Bactiguard®) devices in critically ill patients. And establish the incidence of ICU-acquired sepsis in the most severe critically ill patients in Brazil.

2.1) Objectives

Primary objectives:

- To assess feasibility of the simultaneous insertion of coated and uncoated ETT, CVC and UC in recently admitted critically ill patients without previous invasive devices in a randomized controlled trial.
- To determine how many patients admitted to the ICU will require CVC, ET and UC insertion and, of those, how many will develop sepsis from 48 hours after randomization until day 28 after randomization or until ICU discharge.

Secondary objectives (clinical outcomes):

- Occurrence of nosocomial sepsis up to 28 days after randomization in control (uncoated devices) versus intervention (coated devices) groups
- Combined endpoint of any of the following infections occurring during ICU stay: Ventilator associated pneumonia (VAP), Catheter related bloodstream infection (CRBSI) and Catheter associated urinary tract infection (CAUTI).
- Occurrence of each nosocomial infection individually (VAP, CRBSI, CAUTI) in both groups and rates of positives cultures at each site.
- ICU and Hospital mortality in both groups.

3. Study methods

The full methods section, including detailed intervention and eligibility (inclusion and exclusion criteria), is explained in the Protocol.

3.1) Trial design

Pilot exploratory, randomized, open label, controlled trial. Critically ill patients which will demand placement of invasive devices for organ support (endotracheal tube, central venous catheter and urinary Foley catheter) will be randomized 1:1 to receive coated (Bactiguard®) or habitual (non-coated) devices.

3.2) Method of randomization and concealment allocation

Randomization list will be electronic generated using appropriate software and will be done in blocks stratified by site and by the presence of sepsis at randomization. Allocation group will only be informed after patient register in the electronic database, thereby preventing the investigator of anticipating for which group the patient will be randomized. Due to technical reasons, there will be no blinding.

3.3) Outcomes

The analysis of the two main outcomes involves both the feasibility of the study and the need to obtain epidemiological data on the occurrence of nosocomial sepsis after ICU admission. The feasibility will be assessed by study recruitment rate and by local input on the challenges of the randomization process. We expect a recruitment rate of approximately 1.3 patients a month per site.

Sepsis will be defined as the occurrence of infection plus presence of organ failure, assessed by the Sequential Organ Failure Assessment (SOFA) score (Singer, JAMA 2016; Vincent, Intensive Care Med 1996). The presence of infection with an increase in SOFA score in at least two points will be considered as sepsis (Singer,

JAMA 2016). Sepsis will be further classified as probably related to devices or non-related to the devices after adjudication. Sepsis non-related to the devices will be those where an obvious source of infection that is not related to the devices and is present at device insertion or when the time between device insertion and sepsis diagnosis is less than 48 hours. Obvious sepsis sources unrelated to the devices include: Meningitis, soft tissue infections away from the puncture site (i.e., necrotizing fasciitis), intrabdominal infection and surgical wound infection. An introduction of a new antibiotic class will be used to trigger investigation.

VAP will be defined considering the classic diagnostic criteria (Kalanuria, Crit Care 2014):

1. New or progressive radiographic consolidation or infiltrate. In addition, at least 2 of the following:
    a. Temperature > 38 °C
    b. Leukocytosis (white blood cell count ≥ 12,000 cells/ mm3) or leukopenia (white blood cell count < 4,000 cells/mm3)
    c. Presence of purulent secretions

CRBSI will be defined if **one** of the following is present plus criteria for identifying the catheter as the source (ECDC, 2013):

1. Patient has a recognized pathogen cultured from one or more blood cultures, and the pathogen is not related to an infection at another site. **OR**
2. Patient has at least one of the following signs or symptoms: fever (>38.0°C), chills, or hypotension, and the pathogen is not related to an infection at another site or, if the organism is a common commensal, it must be present from two or more blood cultures drawn on separate occasions. **AND**
3. Culture of the same organism from both the catheter tip and at least one percutaneous blood culture
4. Culture of the same organism from at least two blood samples (one from a catheter hub and the other from a peripheral vein or second lumen) meeting criteria for quantitative blood cultures (at least 5 times greater in

catheter blood) or differential time to positivity (at least 2 hours earlier in catheter blood).

Therefore, for CRBSI to be diagnosed, patient must have criteria 1 OR 2 plus 3 OR 4.

Finally, CAUTI will be defined if **all** the following are present (Nicolle, Antimicrob Resist Infect Control 2014):

1. One or more organisms are present at quantitative counts $\geq 10^5$ colony-forming units/mL from an appropriately collected urine specimen
2. The attending physician believes there is an acute infection and prescribes antibiotics
3. There is no other plausible source of infection at the time the diagnosis of CAUTI is made

The number of antibiotic free days at 28 days will be defined as 28 less the number of days the patient received antibiotics.

All events will be adjudicated by the coordinating center.

3.4) Sample size

This is a pilot study including 100 unique patients. The density of incidence of sepsis and other device-related infection (VAP, CRBSI and CAUTI) will be calculated as the number of events over the total number of patients/day at risk. For the primary outcome of incidence of sepsis, this sample size will be able to inform 95% credible intervals with approximately 3 events per 100 patient-days overall (4 events per patient-day per group), and interval length based on Bayesian *Poisson* regression model with intercept parameter assuming non-informative normal prior centered in 8 event per 100 patient-days incidence rate, $N(e^{0.08}, 5)$.

The prior has a very large standard deviation, giving virtually no importance to its average choice, which was established assuming a slightly worse scenario than was described for a European population of 5 events per 100 patient-days (Allegranzi, 2011).

4. Analyses set

Study protocol mentioned that analysis will be done considering the intention to treat principle. However, during study conduction, some randomized patients did not require simultaneous insertion of all three devices (ETT, CVC and UC) due to illness severity, or the attending physician decided not to insert the devices. Those cases were excluded from the analyses. Consequently, main analysis will be carried out considering a Per Protocol Set (PPS) above. Our expectations are that per protocol and full compliance sets will be the same. Nevertheless, if it happens otherwise, full compliance set must be used to evaluate efficacy measures (infection incidences) and per protocol set to evaluate security measures (adverse events).

4.1) Per Protocol Set

All patients that were randomized, fulfill all inclusion and exclusion criteria, and receive the three devices (ETT, CVC and UC) from allocated arm (coated or habitual) at least one time.

4.2) Full compliance set

All patients that were randomized, fulfill all inclusion and exclusion criteria, and receive the three devices (ETT, CVC and UC) from allocated arm (coated or habitual) all the times that were needed.

5. Analyses Methods

Continuous data will be reported as mean (standard deviation) or median (quartiles) as appropriate. Categorical variables will be described by absolute and relative frequencies.

5.1) Baseline characteristics

Patients' baseline characteristics will be presented without any hypothesis test comparing patients allocated to Coated versus Habitual devices.

5.2) Primary outcome

As described at section 3.4 (sample size), the primary outcome of incidence of sepsis, will be estimated via Bayesian *Poisson* regression model with intercept parameter assuming non-informative normal prior centered in 8 event per 100 patient-day incidence rate, $N(e^{0.08}, 5)$.

5.3) Exploratory outcomes

The same Bayesian *Poisson* regression model with intercept parameter assuming non-informative normal prior centered in 8 event per 100 patient-day incidence rate, $N(e^{0.08}, 5)$, will be done to estimate other infection incidences (VAP, CRBSI, CAUTI).

Besides, the same model will be use to compare patients that used coated devices versus habitual devices. Results will be reported as Risk Ratios (RR) with 95% Credible Intervals. Models will be adjusted for admission type, baseline SOFA and the stratification variable (presence of sepsis at randomization).

Results will be reported considering adjudicated events and events reported by the centers. Sepsis, as reported by centers will be considered as: two point increase in SOFA plus newest use of ATB. The end of sepsis will be considered at the time of ATB withdrawal concomitant with any improvement in SOFA.

Based on those models, we will run simulations to explore scenarios for a larger trial.

5.4) SOFA

We intent to evaluate SOFA during ICU stay using hierarchical Bayesian linear regression models assuming intercept and slope hierarchical effects to patient to include individual time dependence, adjusted for baseline SOFA, and interaction of time and allocated device (coated or habitual). All priors shall be non-informative Normal distributed.

We may also test some nonlinear relation of SOFA on time in each group using polynomial or natural cubic splines. And evaluate alternatives to control death censoring (REF - http://dx.doi.org/10.1136/bmj.j5748) if mortality seems different between arms.

Results will be presented with proper graphs to highlight SOFA variation on time.

5.5) Subgroup analysis

Subgroup analysis will be tested by including interaction effect parameter into the model previously described in section 5.3. The only planned subgroup variable is the stratification characteristic: presence/absence of sepsis at admission.

5.6) Safety and Adverse Events

All reported Safety and Adverse events as described in the protocol will be presented with absolute and relative frequencies and tested with regular Fisher exact test between study groups (Coated vs. Habitual devices).

5.7) Missing data and imputation

We expect minimal missing data; none data imputation is planned.

6. Statistical software

Analyses will be done using R software (R Core Team, 2019). Bayesian models will be adjusted using *rstan* package (Stan Development Team, 2019).

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