Study title

Observational retrospective analysis assessing the influence of three compartment bags (3CBs) compared to hospital compounded parenteral nutrition bags on blood stream infections

Study number

3CBs-001-CNI (CT.gov ID NCT03284398)

Study rationale

PN requirement

Nutritional support is often needed in critically ill patients with parenteral nutrition (PN) required in approx. 15% [Ziegler 2009]; in most patients requiring PN nutritional needs are met by standardized formulations recommended by European and US guidelines [Kochevar 2007, Singer 2009].

PN types: compounding vs multichamber bags

PN solutions are derived from

- manual compounding of bags in hospitals with or without the use of laminar-air-flow systems as all-in-one solutions
- industrial, standardized multi-chamber bags (MCB), e.g. SmofKabiven® and Kabiven®.

Complications of PN

PN is an independent risk factor for catheter-related bloodstream infections (BSI) [Beghetto 2005], a common cause of morbidity and mortality with substantial healthcare-related cost.

BSI rates are strongly influenced by

- the delivery system with a significantly higher incidence in patients receiving hospital compounded PN bags compared to MCBs [Turpin 2012, Pontes-Arruda 2012]
- the type of compounding with automated compounding being superior to manual compounding reflected by lower BSI
- manipulations despite compounding under strict sterile and aseptic conditions with an increased risk of errors and sepsis [Singer 2009]
- addition of nutrients to the PN system on the ward [Turpin 2014].

Commercially available, standardized MCBs avoid the need of compounding, thereby reducing the risk of BSI. Within the MCBs, the three chamber bags (3CBs), e.g. SmofKabiven® and Kabiven® require least additional manipulations as all three main compartments consisting of amino acids, glucose with electrolytes, and lipids are pre-filled.

Required data for three chamber PN bags

To date, there is only scarce evidence showing reduced frequency of BSI with three chamber bags such as Fresenius

	Kabi's SmofKabiven® and Kabiven® compared to hospital compounded PN bags. This information is relevant to provide data for the pharmaco-economic model to support the clinical and economic values of three-chamber bags.
Hypothesis	Patients receiving 3CBs experience a significantly lower BSI rate compared to patients receiving hospital compounded PN bags.
Objectives	**Primary objective** Assess the rates of BSI from the use of 3CBs (e.g., SmofKabiven®, Kabiven®, others) compared to hospital compounded bags (HCBs) in patients requiring PN in Spanish hospitals **Secondary objectives** - Determine the extent of treatment requirement in patients receiving 3CBs compared to hospital compounded bags - Assess mortality rate in patients receiving 3CB compared to patients receiving HCBs - Evaluate the influence of additions made to the PN bags on BSI rates - Assess the effect of manual versus automated compounding on BSI rates - Evaluate the rate of PN-associated adverse events in patients receiving 3CBs compared to HCBs, including sepsis, organ failure, metabolic impairment, hepatic dysfunction and electrolyte imbalance - Assess the achievement of the nutritional target in patients receiving 3CBs compared to HCBs
Investigational sites	Approximately 10 sites using 3CBs and/or HCBs
Study design	Retrospective observational data retrieval in a two-step design: In step 1, data from 30% of the target patient number will be obtained from the investigational sites to evaluate study feasibility and perform an interim analysis assessing statistical power.In step 2, the study will be continued by documenting further 70% of patients if the statistical power is > 60%.
Observational drug	Any PN administered in 3CBs, containing all three major macronutrients (glucose, amino acids, lipids)
Comparator	Hospital compounded PN bags containing all three major macronutrients
Patients	Adult hospitalized patients receiving PN in Spain, treated on any ward and by any medical discipline within the hospital (intensive care unit, normal ward; surgery, non-surgery)

Outcome parameters

Primary outcome parameter

- BSI only with concomitant antimicrobial treatment (bacteria and/or candida), thereby excluding patients with contaminations

Secondary outcome parameters

- Rate of peripheral line associated BSI
- Rate of central line associated BSI
- Single organ failure, multiple organ failure
- Mortality
- PN-related adverse events of special interest: metabolic impairment (hyperglycemia, hypertriglyceridemia), hepatic dysfunction (cholestasis: transaminases, gamma-glutamyl transferase, alkaline phosphatase, bilirubin), electrolyte imbalance (sodium, potassium, chloride, calcium, phosphate, bicarbonate)
- Changes in prealbumin, C-reactive protein
- Achievement of caloric target (hypo-, hyperalimentation)
- Extent of treatment requirement: Hospital length of stay, ICU length of stay, antibiotics, antimycotics, vasopressors and mechanical ventilation

These parameters will be documented for the multivariate analysis - if available - and the discussion. These are not outcome parameters:

- Demographic data: gender, age, weight (BMI)
- Admission type: elective, emergency, transferral
- Reason for hospital admission: leading diagnosis
- Reason for ICU admission: surgical, medical, trauma
- Primary disease
- Duration of hospitalization before venous catheter (VC) placement and PN
- Type of venous access: central, peripheral
- VC insertion and maintenance according to "Bacteremia Zero" protocol
- Type of hospital compounding: automated, manual
- VC related influence: number of VC; number of lumen of VC; site of VC placement (jugular, subclavian, femoral); insertion of VC in ER, OR, ICU; clinical experience of staff placing and handling VC and PN; duration of VC; duration of PN and duration between VC placement and PN; SOP for hygiene in place (cap, mask, sterile gloves sterile full body drape)
- Indication for PN
- Percentage of PN (supplemental PN, total PN)
- Omega-3 fatty acids and glutamine as active ingredients

- Additions of vitamins, trace elements and/or electrolytes to PN bag
- Addition to PN bag made under sterile conditions in the pharmacy, or on the ward
- Co-morbidities: cancer, malabsorption, pancreatitis, liver failure, renal failure, diabetes, malnutrition (SGA), gastrointestinal disorder
- Enteral, oral nutrition, oral nutritional supplements
- Antibiotic and antimycotic treatment (number, duration, antibiotic free days)
- Availability of a Nutrition Support Team at the center
- Hospital characteristics: region, teaching status, urban/ rural, number of beds
- APR-DRG severity of illness
- APACHE II score or SAPS II score

Inclusion criteria

General:

- Adult patients ≥ 18 years
- Hospitalized between 1. January 2014 and 31. December 2015

Study-specific:

- PN for at least three consecutive days
- PN as 3CBs or hospital compounded, containing all three major macronutrients
- complete medical record regarding treatment information, PN administration details and, if applicable, adverse events

Exclusion criteria

General

Prior participation in this study

Study specific

- BSI at admission to the participating hospital (not hospitalacquired), i.e., prior to the 3rd calendar day of admission

  where day of admission is calendar day 1
- Immunosuppression due to concomitanttherapy (e.g. immunosuppressive therapy due to transplantation, use of glucocorticoids)or disease (e.g. HIV, leukemia)
- persisting vascular access (port, shunts for dialysis) used during PN episode
- femoral venous placement of central venous line
- burns (irrespective of severity), extensive skin injuries (e.g., Lyell´s disease)
- chemo-/ radiotherapy during hospital admission period or up to 3 months before hospital admission
- change of PN delivery method during study period, e.g., from compounding to 3CBs (change of dosing and/or frequency during the observational period is allowed)

Sample size

The sample size must allow the comparison of BSI rates associated with three chamber bags with those associated with hospital compounded bags. Due to the high variability among studies reported in the literature, a mean scenario is considered based on the incidence of BSI infections reported in Spain [Bonet 2005; Aguilella 2012], i.e., an overall incidence of BSI of 12.3% with a difference between the groups of 3% (± 1.5%). Samples size are estimated assuming incidence rates of BSI in MCB of 10.8% and 13.8% in hospital compounded PN, respectively.

A sample of 1891 patients per PN type (3782 patients in total) is required taking into account a significance level of 0.05, the influence of the interim analysis on statistical power, and a statistical power of 0.80.

Statistical analysis

Interim analysis: The study is run in a 2 stage group sequential design with an interim analysis (IA) after acquiring 30% of the total sample size. This allows a premature discontinuation if BSI rates and their difference, i.e., the actual power of the study, are substantially lower than planned. The study will be terminated after the IA if the conditional power based on the IA results will be smaller than 60%.

Final analysis: Baseline demographics, co-morbidities and hospitalization characteristics will be reported descriptively by means of standard deviations and medians with ranges for continuous variables and by counts and percentages for categorical variables. Incidence rates for BSI will be reported by treatment group.

Multivariate logistic regression will be used to create a model to estimate the risk of BSI. The model will be adjusted for covariables as risk factors, potential confounders, baseline differences, etc. As variable-selection method correlations will be calculated for the rough selection and then backward elimination selection will be applied in the logistic regression model with a significance level of 10%. The risk of BSI will be reported as adjusted odds ratios with 95% confidence limits. For secondary/ further variables multivariate regression models will be used.

Observation period

Length of stay at the participating hospital

Planned start and end

Data retrieval for step 1: September 2016 – January 2017
Data retrieval for step 2: March – June 2017

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