Centro Hospitalar Trás-os-Montes e Alto Douro

STATISTICAL ANALYSIS PLAN

The impact of carvedilol posology on Clinically Significant Portal Hypertension: Insights from Elastography Measurements

31 May 2023

Participants and methods

Study Design

The present study was an experimental study conducted at the Liver Unit at Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal. Patients with CSPH considered responders to carvedilol prescribed twice daily were included. These patients had their SSM and LSM measured through TE after suspending their second daily carvedilol intake. Results from the SSM were compared with the values measured while under treatment and before being prescribed with carvedilol. Additionally, comparisons for under treatment with carvedilol and 24-hour suspension were stratified according to carvedilol daily dosage, *D'Amico* classification, the Model for End-stage Liver Disease (MELD) scores, Child-Pugh score, and aetiologies for PH. The same procedure was repeated for the results of LSM. This study was approved by the clinical research ethics committee of Centro Hospitalar de Trás-os-Montes e Alto Douro, in accordance with the 1975 Declaration of Helsinki declaration.

Participants

All patients over 18 years of age, followed at the Liver Unit at Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal for CSPH (defined as a LSM $\geq$ 25 kPa or SSM over 45kPa prior to introduction of carvedilol) were eligible. Patients were excluded from the study if they were non-responders to NSBB (defined as a reduction of their SSM of less than 10%), were under treatment with any NSBB other than carvedilol, had a dosing regimen other than twice daily, had not been performed a SSM or LSM through TE while under treatment within 3 months prior to the beginning of the study, were obese (body mass index (BMI) > 30 m/kg^2), had contraindications to NSBB use, presented portal venous thrombosis or refused to participate in the study.
Eligible patients were contacted by telephone up to 3 days prior to their appointment and assessed for enrolment. Patients were asked to suspend the night dose of carvedilol and postpone the morning dose until LSM and SSM were measured. After enrolment, patients could be excluded from the study if they failed to comply to the study regimen (last dose of carvedilol within 24 hours or related with TE protocol, namely overnight fasting), evaluated during their appointment. Informed consent were obtained from each patient included in the study.

Data Collection

For each patient, data on gender, age, aetiologies for CSPH, D'Amico classification, the Model for End-stage Liver Disease (MELD) scores (both MELD-Na, and MELD 3.0), Child-Pugh score, and carvedilol daily dosage were collected (22-25). For CSPH due to cirrhosis, the diagnosis of cirrhosis was based on previous biopsies or compatible clinical, biochemical, and imagiologic findings.

LSM and SSM were assessed by TE using FibroScan® 630 Expert (Echosens, Paris, France)

and values were obtained according to the recommendations of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) (26). For each patient, LSM and SSM values were considered adequate if the interquartile range (IQR) was < 30% of the median value. The values were obtained, after overnight fasting, with the patient in a supine position with maximal abduction of the left arm; the probe was positioned in an intercostal space where the spleen was correctly visualized by US. LSM and SSM were expressed in kilopascal (kPa).

Data on the most recent TE in the previous 3 months and the TE performed before introduction of carvedilol were also collected through the electronic medical records of the enroled patients.

Blood chemistry tests were also performed during the appointment and results on haemoglobin, platelets, albumin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, gamma-glutamyltransferase (GGT), total and direct bilirubin, sodium, creatinine and international normalize ratio (IQR) were collected.

Sample Size

The sample-size calculation was based on the assumption of a SSM of 35.8 kPa during treatment and a detectable increase of 35.0% (48.3 kPa) while supressing one dose of carvedilol (1). We considered standard deviation as 19.2 kPa, an alpha of .05 and a power of .80. We also assumed that 10% of enroled patients might fulfil further exclusion criteria, by not following the study proposed regimen, totalling 33 patients needed to enrol in the study.

Data Analysis

Categorical variables were described with absolute and relative (%) frequencies and continuous variables were described with means and standard deviations (SD) when approximately normally distributed or with median an interquartile range (IQR) otherwise. Results from the SSM evaluation through TE at appointment were compared with the values measured before introduction of carvedilol and in the previous TE evaluation within 3 months, using paired t-tests. Further comparisons between SSM at appointment and within the previous 3 months were made stratifying for aetiology of portal hypertension, *D'Amico* classification, the Model MELD scores, Child-Pugh score, and carvedilol daily dosage. For the described analysis, aetiology was divided in alcoholic cirrhosis and non-alcoholic cirrhosis; in quartiles for MELD and Child-Pugh; and in above and below the median for carvedilol daily usage. The same procedure was repeated for LSM.

Data analysis was performed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). 95% confidence intervals (CI) for point estimates were calculated. P-values <.05 were considered statistically significant.