Psychological Support Based on Positive Suggestions (PSBPS) on Mental Health Morbidity and Cognitive Function

NCT04045210

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Study Protocol and Statistical Analysis Plan

The study was approved by the Institutional Review Board (19-004660) and registered on clinicaltrials.gov (NCT04045210) prior to the first patient enrollment.

Study design and setting

We conducted a single-center, prospective, randomized, controlled trial comparing the effect of PSBPS vs. no PSBPS on psychological and cognitive outcomes and health related quality of life in the ARF population. At the study onset two psychiatrists at our institution expressed interest to undergo PSBPS training based on the abovementioned method designed for lay health care professionals and donate their time to the study. Therefore, we initially planned to conduct a 3-arm trial with patients randomized 1:1:1 to intervention by psychiatrist, ICU doulas, and usual care, stratified by ICU location. Eligible patients were admitted to an adult ICU in a tertiary care center between September 2019 and December 2024. In November 2021 randomization was changed to 1:1 to intervention by ICU doulas vs usual care, stratified by ICU location, as one of the study psychiatrists left the institution, and it was not feasible for the remaining psychiatrist to carry the entire study arm solely on his own. Aso, as the doulas were sometimes not allowed to enter the hospital during COVID-19 lockdowns, we had to improvise by attempting to deliver the intervention using a tela-doc – a telehealth platform using an ipad.

Participants

Inclusion criteria were adults (age $\geq$18) admitted to an ICU, requiring mechanical ventilation and expected to stay $\geq$48 hours. Exclusion criteria included a history of dementia, acute alcohol/substance abuse or withdrawal, admission following a suicide attempt, psychotic disorders such as schizophrenia, patients with a recent ICU admission (within 6 months), incarceration, severe metabolic encephalopathy, status epilepticus, non-English speaking, and patients not expected to survive their hospital stay or who were receiving only symptomatic treatment at the end of life. Eligible patients were systematically screened daily Monday through Friday using electronic medical record review; those meeting inclusion criteria were approached once feasible following ICU arrival. Informed verbal consent was obtained by a study coordinator from a legally authorized representative. Once the patient was able to interact, continued study participation was verified with them as well. Both intervention and controls continued to receive standard medical care at the discretion of the ICU team. The intervention arm also receive PSBPS as soon as feasible following intubation daily. Doulas also were instructed to liaise with family, the team, and with the nursing staff.

Measurements

Baseline demographics (including prior psychiatric history, substance abuse, education level), comorbidities, and ICU stay data (duration of ventilation, length of stay, delirium-free days, use of neuromuscular blockers and steroids, type and cumulative dose of a sedative/analgesic, number of physical/occupational therapy sessions, serial data on blood pressure, oxygenation, blood glucose, disease severity, and organ systems affected) were obtained pragmatically through electronic health record (EHR) abstraction. Questionnaires: HADS-A, HADS-D, IES-R, and EQ-5D-3L were collected to assess metrics of anxiety, depression, and acute stress; MoCA-blind was used to assess cognitive outcomes. Study patients were then contacted 3 months after hospital discharge to repeat assessments by phone.

Sample size

Power and sample size were originally calculated based on the three-arm trial with 1:1:1 randomization to Psychiatrist, Doula, and Standard Care arms. A 2-point difference in HADS-A was determined to be a minimum clinically relevant difference to detect for the current study. In preliminary studies, we observed mean (standard deviation (SD)) HADS-A score 7.7 (3.9) in-hospital post-ICU discharge and 5.3 (4.0) at 3 month follow up. Assuming a pooled standard deviation of 4.0, n=64 participants per arm (n=192 total) would achieve 80% power to detect a difference of 2 units using a two-sided two-sample t-test at alpha=0.05. We estimated that 20% of participants who complete in-hospital questionnaires would drop out prior to follow up. Thus, we planned to enroll and randomize until n=240 participants completed in-hospital questionnaires. Power reflects a pairwise comparison of Doula versus Standard Care and similarly Psychiatrist versus Standard Care.

Calculations for this study assumed no multiple testing correction for multiple arms or for several outcomes evaluated in order to maximize power across all comparisons to detect clinically relevant differences that could be evaluated in future confirmatory multicenter study.

The trial was modified for reasons described previously to drop the Psychiatrist arm. This decision was made without evaluation of study outcomes by treatment arm (no interim analysis was performed). We also observed greater dropout at follow up than anticipated in the total sample. The study was modified to a 2-arm trial with a plan to enroll until 182 total participants have been randomized and completed post-ICU discharge assessments (91 per the two active arms) to allow for 30% dropout by the 3 month follow up assessment.

Statistical Analysis

Continuous data are described using median (25^{th}, 75^{th}) percentiles and categorical data using n (%). Outcomes are descriptively compared amongst arms using Kruskal-Wallis tests or Wilcoxon rank-sum tests for semi-continuous or ordinal outcomes and chi-square tests for nominal categorical outcomes.

The study followed a per-protocol analysis principle. Participants were included in the analysis and analyzed according to their randomized arm if, for Doulas and Psychiatrist arms, they received at least two sessions of the assigned intervention. For in-hospital questionnaires, participants completing at least one questionnaire were considered sufficiently adherent to the protocol for the analysis of all in-hospital questionnaire outcomes. For the follow up questionnaires, subjects completing at least one questionnaire were considered sufficiently adherent to the protocol for the analysis of all follow up questionnaire outcomes. There were no other protocol violations resulting in the exclusion of participants from analysis.

HADS-A score at the in-hospital, post-ICU discharge timepoint was compared between the three study arms using Analysis of Covariance (ANCOVA) adjusting for age, sex, and ICU location. ICU location was included for adjustment since it was a randomization strata. Age and sex were additionally selected in the analysis plan as variables likely associated with outcomes that would increase power to reject the null hypothesis of no treatment effect under the ANCOVA analysis model. We report two pairwise comparisons of Doula versus Standard Care and Psychiatrist versus Standard Care, reporting the adjusted mean difference in HADS-A between arms with 95% confidence interval. The same approach was taken for HADS-D, IES-R scores, and MoCA. A proportional odds regression was used for ordinal EQ-5D-3L outcomes, with adjustment for age, sex, and ICU location. We report an odds ratio and 95% confidence interval where the odds ratio reflects whether the intervention arm causes higher odds of a worse (more problems) EQ-5D-3L outcome compared to Standard Care. The same methods were used for analysis of 3-month follow up outcomes.

Missing data were present for many outcomes at both timepoints. We used multiple imputation for missing values of IES-R outcomes (intrusion, avoidance, hyperarousal), MoCA, and EQ-5D-3L (mobility, self-care, usual activity, pain/discomfort, anxiety/depression) for in-hospital and 3-month follow-up questionnaire responses. HADS-A and HADS-D scores were fully observed without missing data. Twenty-five imputations were performed using predictive mean matching under the assumption data may be Missing At Random possibly related to other observed outcomes at either timepoint or baseline patient characteristics or hospital stay characteristics including treatment arm, age, sex, hospital stay (days), ICU stay (days), marital status, education status, ICU location, use of vasopressors, use of paralytics, use of BiPAP, history of depression, and history of anxiety. Analysis models were run on each imputed dataset and results aggregated to account for uncertainty due to missing data.

Two-tailed p-values of 0.05 or less were considered statistically significant. There were no adjustments for multiple comparisons for reasons given previously. Data management, multiple imputation, and analyses were completed with SAS version 9.4 (SAS Institute, Cary, North Carolina).