

## ABSTRACT

### **Abstract**

**Introduction:** In critical illness, adverse emotions, anxiety and pain influence patients' psychological and physiological outcomes. When humans experience stress, specific stress-related neuropeptides are released into the hypothalamohypophyseal and systemic circulation including neuropeptide Y.

**Aim:** In critically ill patients, we aimed to:

1. Investigate the effects of a composite integrative psycho-cognitive nursing intervention on a) pain, anxiety, calm/relaxation levels and perceived quality of sleep, b) arterial blood pressure, heart rate, respiration rate, c) disease severity, morbidity, mortality and length of stay and d) serum levels of the stress-related neuropeptide Y (NPY) and of the inflammatory/ apoptotic marker fasL, and
2. Explore the association between neuropeptide Y and a) pain and anxiety levels, c) disease severity, mortality and c) fasL, in patients receiving the intervention compared to patients receiving standard care only.

**Methods:** A single-blind randomized controlled trial design was employed with sixty general ICU patients randomized to an intervention (N=30) or standard care group (N=30). The 60-min intervention consisting of presence, touch/massage and relaxation, guided imagery, and music listening, was delivered individually every morning for up to 5 days. Eligibility criteria included age  $\geq 18$ , Glasgow Coma scale (GCS)  $\geq 9$  and understanding Greek. Patients were assessed in the mornings, pre- and post- intervention. Outcome measures included pain ratings [3 scales: 10-point numeric rating scale (NRS,

self-reported and observer), behavioral pain scale (BPS), critical-care pain observation tool (CPOT)] and self-reported anxiety, relaxation/calm and quality of sleep (10-point NRS). NPY and FasL levels were measured pre- and post- intervention on days 1, 3 and 5. Patients' disease severity was assessed by the Multiple Organ Dysfunction Score (MODS) and Sepsis-related Organ Failure Assessment (SOFA) as well as by the APACHE II, Richmond Agitation-Sedation Scale (RASS) and GCS. Serum levels of NPY and FasL were quantified by an enzyme-linked immunosorbent assay (ELISA). Statistical analysis included Analysis of Covariance (ANCOVA) (adjusting for pre-treatment measurements and other characteristics) and Linear mixed models (LMM) analysis. Comparisons between the intervention and control group at each time point and each day of study were assessed using a t-test and the effect size Cohen's d.

**Results:** At baseline, no significant differences between study groups were noted. In the intervention group, significant decreases in CPOT pain ratings compared to the control group were observed over time for the 5-day follow up period ( $p < 0.008$ ), even after adjusting for confounders (age and gender,  $p < 0.001$ ). There was also a reduction from pre- to post- intervention measurements on each day. 1st day post- intervention, CPOT ratings in the control group ( $2.5 \pm 1.29$ ) vs. the intervention group ( $1.44 \pm 1.26$ ;  $p = 0.004$ ) suggest a strong effect size of the intervention (Cohen's  $d = 0.83$ ). Analysis of Covariance (ANCOVA) with 1<sup>st</sup> day post- intervention CPOT ratings and adjustment for disease severity, analgesics and pre-intervention pain levels, showed a significant difference in the mean pain level in the intervention group ( $p < 0.001$ ) Similar trends were observed with other pain scales as well. The intervention group also exhibited significantly

increased relaxation/calm levels ( $p < 0.001$ ) and decreased anxiety levels ( $p = 0.03$ ) and decreased systolic blood pressure levels post- intervention over time ( $p = 0.008$ ). Anxiety ratings exhibited a positive association with pain ratings ( $p < 0.001$ ). A significant effect in improving perceived quality of sleep was also observed in the intervention group ( $p = 0.016$ ). Mean NPY post- intervention levels in the intervention group ( $0.71 \pm 0.14$ ) were significantly lower than in controls ( $1.19 \pm 0.45$ ) ( $t = 2.95$   $p = 0.012$ ) with a high effect size (Cohen's  $D = 1.12$ ). A statistically significant effect of the intervention on NPY levels was observed over time ( $p = 0.024$ ) even after adjustment for disease severity (SOFA and MODS) ( $p = 0.038$ ). NPY levels were positively associated with fasL levels ( $p < 0.001$ ), but neither was associated with SOFA and MODS scores.

**Conclusions:** The results of this randomized clinical trial, support the hypothesis that a composite supportive nursing intervention including massage, relaxation, imagery and music listening may improve critically ill patients' physiological and psychological outcomes and experience of care. Furthermore, based on these results, it is probable that the favourable effects of the intervention are associated with decreased released of stress-neuropeptide levels, whereas, the effect on the inflammatory/ apoptotic marker fasL remain inconclusive. Further study is needed to standardize components of the composite intervention that may account for the largest proportion of the effect. The study of stress neuropeptides may provide further insight for the development and evaluation of psychodynamic holistic interventions for improving critically ill outcomes.