Effects of critical care-related stressors on physiological stress response markers: a pilot study

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SUMMARY

- Critical illness is associated with high stress levels. Nursing procedures may impose additional stress or even modulate the stress response; however, their effects on stress biomarkers have not been addressed.
- The aim of this study was to explore the effect of common critical care stressors (endotracheal suctioning, bed bath, pressure injury) on serum biomarkers of the stress response (adrenocorticotropic hormone, cortisol, prolactin, neuropeptide Y and substance P) in severely critically ill adults.
- A pilot exploratory correlational design with repeated measures in a convenience sample of consecutive adult critically ill patients was used. Linear mixed modelling was used to account for repeated measurement fashion, after adjustment for the presence of pain, opioid analgesia and disease severity. Neuropeptide levels were quantified by an electrochemiluminescence immunoassay or by commercially available enzyme-linked immunosorbent assay kits.
- We observed: a significant association between bed bathing and increased prolactin and decreased substance P levels even after adjustment of the aforementioned confounders ($p < 0.05$), b) an association between pressure injuries and increased neuropeptide Y, even after adjustment for pain ($p < 0.05$), c) no significant associations between endotracheal suctioning and stress neuropeptides.
- These novel results raise the possibility that nursing interventions and pressure injuries may modulate stress responses in critically patients. Therefore, these conditions need to be taken into account when evaluating the stress response in critical illness. More study is needed to elucidate the clinical significance of these findings.

INTRODUCTION

Critical illness can be very stressful to individuals and families and has been linked to short and longer-term psychological alterations and the post-traumatic stress disorder (Davidson et al., 2013). Additionally, care in the intensive care unit (ICU) includes a variety of routine nursing interventions, such as hygiene procedures (bathing, oral and skin care), mobilization and positioning, to prevent complications and to improve patients' outcomes (Gunn & Fowler, 2014). Recent evidence suggests that such interventions may impose more stress and pain to patients (Puntillo et al., 2014). With the increasing interest in non-pharmacological approaches to treat common alterations in critical illness (Barr et al., 2013), researchers can assess a variety of biomarkers of the stress response, as part of the exploration into the physiological effects of integrative approaches, such as music, massage or relaxation and guided imagery (Papathanassoglou & Park, 2016). It is well established that a number of physiological stress and pain responses, including a predominant hypothalamus-pituitary-adrenal (HPA)-axis response, result in the release of multiple biomolecules such as adrenocorticotropic hormone (ACTH), cortisol, neuropeptide Y (NPY) substance P (SP) and prolactin (Lupien et al., 2007; Mpouzika et al., 2013). However, the modulating effect of routine nursing interventions and common ICU stressors on the stress response of critically ill individuals has not been addressed. The study of such modulating effects is important in: a) elucidating the potential therapeutic effect of routine nursing interventions, and b) clarifying confounding and mediating variables in order to further research in critical illness stress. Comfort and relaxation feelings, as well as painful and stressful lived experiences, induced by different nursing and therapeutic interventions in the ICU, along with the related neuropeptidic responses may impact short- and longer-term physiological and psychological outcomes in these patients and, thus, merit investigation.

LITERATURE REVIEW

A variety of nursing interventions are performed in the ICU, including bathing and suctioning. Bathing promotes hygiene and gives the opportunity for communication between the nurse and the ICU patient, through verbal, eye and tactile contact. Moreover, it gives nurse an opportunity to re-orientate the patient providing him/her information and connecting him/her to the reality. Additionally, it promotes relaxation through massage movements performed to the immobilized limbs and body, which maximize comfort. Research data have shown promotion of relaxation feeling and reduction of agitation levels, in geriatric patients after bathing (Martin et al., 1999;

Sloane et al., 2004). Suctioning, on the other hand, has been shown to be related to increased pain levels in awaked critically and acutely ill adults (Arroyo-Novoa et al., 2008), in brain injury patients (López-López et al., 2014) and in neonates (Anand et al., 2005).

Pain and other stressors, activate the HPA-axis response, resulting in the release of ACTH and cortisol. HPA-axis activation is markedly influenced by the intensity of the triggering stressor (Belda et al., 2016). Moreover it has been shown that different neuropeptides such as NPY and prolactin are involved in different stressful and painful situations (Lupien et al., 2007; Mpouzika et al., 2013). More specifically, NPY levels are increased in response to reduced cortisol levels (Carvajal et al., 2006) and research data have demonstrated an association between NPY and stress whereby primarily plasma NPY levels decrease in stressful situations (Kormos & Gaszner, 2013). Under painful conditions NPY levels are increased (Magnussen et al., 2015). Additionally, the role of prolactin after exposure to different stressors is well established in humans as well as in animal models (Gala 1990, Sobrinho 2003). Prolactin serum levels are significantly increased, after exposure to acute psychosocial stress, along with increased plasma cortisol, serum ACTH, in response to the stressor (Lennartsson & Jonsdottir, 2011). Moreover, it has been shown that prolactin is positively correlated with anger feelings, or lived experiences considered humiliating by the individuals (Sobrinho, 2003).

Substance P is involved in both nociception and stress perception (Iversen 1998). Elevated SP levels appear to associate with psychological stress in humans (Papathanassoglou et al., 2010). Additionally, there is evidence that SP may have a role in sepsis (Beer et al., 2002) and is also involved in inflammation (Bhatia and Moochhala, 2004) and immunity in critically ill patients (Mpouzika et al., 2013).

AIM

This pilot study, aimed to explore the effect of common critical care stressors, including two nursing interventions (endotracheal suctioning, bed bath) and of the presence of pressure injuries, on serum biomarkers of the stress response in severely critically ill adults. Specifically, we assessed the effects of the aforementioned conditioned on serum levels of ACTH, cortisol, prolactin, NPY and SP in a repeated measures fashion, after adjusting for the presence of pain, opioid analgesia and disease severity. This investigation was part of a bigger study on the effects of critical illness on stress and apoptotic biomarkers (Papathanassoglou et al., 2015). In view of recent evidence of altered stress neuropeptide levels in critical illness (Mpouzika et al., 2013; Papathanassoglou et al., 2015) this investigation can shed some light into the factors that need to be taken into account for a potential physiological assessment of stress response profiles in critically ill individuals in the future. A comprehensive assessment of stress in ICU patients may be useful in tailoring supporting interventions and improving psychological and physiological outcomes.

MATERIALS AND METHODS

Research design

We employed an exploratory correlational design with repeated measures. The study received institutional review approval and was performed at a large Metropolitan hospital in Athens, Greece. Patient recruitment took place during a period of one year. Before commencement of study procedures, all patients (or their legal representatives) and control subjects signed an informed written consent.

Study group

A convenience sample of consecutive adult critically ill patients with diverse admission diagnoses was studied. Critically ill patients with sepsis, shock (regardless of etiology), patients with delirium and patients who received corticosteroids were excluded. Blood samples were drawn every 48 hours at 9 am through an arterial catheter for a maximum period of 15 days since admission to the protocol. Nursing interventions occurring within half an hour before acquiring blood samples were recorded.

Neuropeptide levels

Peripheral blood samples were centrifuged at 3000 rpm for 20 min and the serum stored at -20oC. ACTH (pg/ml) and prolactin (ng/ml) levels were quantified by an Electrochemiluminescence Immunoassay (ECLIA) with the Elecsys 2010–Roche analyzer (Roche, Bohemia, NY, USA). NPY levels were quantified by commercially available enzyme-linked immunosorbent assay (ELISA) kits (Phoenix Pharmaceuticals Inc, Burlinngame, USA and Assay Designs Inc, Ann Arbor, USA, respectively). All assays were run in duplicate. Intra-assay coefficients of variation were less than 5%.

Assessment of disease severity and pain

The Multiple Organ Dysfunction Score (MODS) (Marshall et al., 1995), was employed to assess disease severity. Since, most of participants were not able to self-report their pain, we used the behavioural pain scale (BPS) developed by Payen et al. (2001) for critically ill patients (scale range: 3-12), which consists of a sum of scores based on facial expression, upper limb movement and compliance with ventilation (Payen et al., 2001).

Statistical analysis

Variable values were expressed as mean ± standard deviation. In cases of significant departure from normality criteria, logarithmic transformation of variables was performed. A nominal significance level $\alpha = 0.05$, was used.

To explore associations between critical illness stressors and neuropeptide levels accounting for repeated measurements, we used linear mixed modeling (LMM) with and without adjustment for MODS severity, pain and administration of opioid analgesia. LMM allows for time-varying covariates, intra-subject correlation and loss of participant follow-up due to ICU discharge or transfer. We selected the best model fit based on the Akaike Information Criteria (AIC). A nominal significance level $\alpha = 0.05$ was used. Statistical analyses were performed in the Statistical Package for Social Sciences (SPSS version 21).

RESULTS

We enrolled 36 consecutive adult critically ill patients. Participants were caucasian, 75% male with an age 51.55 (SD 18.85) years (see Tables 1a, 1b). Patients received fentanyl or remifentanil intravenous (IV) infusions, and midazolam or propofol for sedation.

Presence of stressors

We recorded interventions that took place within half an hour before blood sampling. We also recorded presence and number of pressure injuries. Interventions within half an hour before blood sampling included 19 instances of bed bath and 36 instances of endotracheal suctioning. Pressure injuries were present in 9 patients. Pain at the behavioral pain scale, accounting for all measurements exhibited a mean score of 3.72 (SD 0.11; range 3-7).

Table 1a. Demographic data and admission diagnoses

Characteristics		n (%)
Gender	Male: female	27: 9 (75: 25)
Admission diagnosis	Surgical/trauma	11 (30.5)
	Neurosurgical	17 (47.3)
	Medical	4 (11.2)
	Cardiovascular	4 (11.2)

Table 1b. Clinical data

Scale [scale range]	1st day	Day of maximum severity	Last day
MODS [0-24] mean score (SD)	4.40 (2.30)	6.33 (2.86)	5.88 (5.5)
APACHE II [0-71]] mean score (SD)	14.80 (5.71)	20.3 (7.26)	19.13 (7.43)
BPS [3-12] mean score (SD)	6.00 (2.82)	6.15 (2.77)	4.72 (1.25)

Table 2a. Bi-variable models for the association between stressors and stress neuropeptides accounting for repeated measurements. CI, confidence interval.

Dependent variable	Parameter	Estimate	95% CI	Significance *p*
Prolactin	Bed bath	0.524	0.04- 1.00	0.032
	Pressure injury	0.293	0.07- 0.60	0.053
Substance P	Bed bath	-0.40	-0.88- -0.08	0.042
Neuropeptide Y	Pressure injury	0.591	0.019-1.17	0.039

Table 2b. Multivariable models additionally adjusting for opioid analgesia and either MODS severity or pain (BPS rating). CI, confidence interval.

Dependent variable	Parameter	Estimate	95% CI	Significance *p*
Prolactin	Bed bath	0.566	0.11-1.02	0.017
	Opioid analgesia	0.433	0.02-1.9	0.049
	BPS rating	0.324	0.45-0.10	0.04
	MODS	0.18	-0.32- 0.89	0.305
Substance P	Bed bath	-0.380	-0.62- -0.19	0.022
	BPS Rating	0.474	0.05-0.87	0.05
	MODS	0.11	-0.01- 0.77	0.333

Association between presence of stressors and stress neuropeptides

We observed no associations between any of the stressors studied and serum levels of ACTH and cortisol. We observed associations between having a bed bath within half an hour prior to blood sampling and increased levels of prolactin ($p < 0.05$). Likewise, we observed associations between having a bed bath and decreased SP levels (see Table 2a). The associations remained significant when we controlled for either disease severity (MODS score) or pain (BPS), but not when adjusting for both pain and disease severity simultaneously (Table 2b). Associations also remained significant after adjusting for administration of opioid analgesia (see table 2b).

We observed no significant associations or noteworthy trends between endotracheal suctioning within half an hour prior to blood sampling and serum neuropeptide levels. With regard to the presence of pressure injury, we observed associations with increased NPY levels, even when adjusting for pain ratings (Table 2a). Also, although not significant, a trend for an association with increased prolactin levels was noted (Table 2a). When accounting for the number of injuries, results were not significantly altered.

DISCUSSION

This study aimed to address for the first time potential associations between critical-care related stressors such as bed bathing, endotracheal suctioning and the presence of pressure injuries and specific stress neuropeptides. We observed: a) a significant association between bed bathing, prolactin and SP when adjusting for either disease severity, pain and opioid analgesics, b) an association between pressure injuries and NPY, even after adjustment for pain, c) no significant associations between endotracheal suctioning and stress neuropeptides. An additional noteworthy finding was that although we observed no alterations in the classical HPA-axis stress hormones (ACTH, cortisol), alterations to peripheral levels of stress neuropeptides involved in the regulation of hypotahalamic responses in stress were still noted. To the degree of our knowledge these results are novel. Based on these observations, the effect of nursing interventions on the stress and neuroendocrine response in critically ill patients may merit further investigation.

The limitations of this pilot exploratory study should be acknowledged. First, the sample was relatively small which may have limited statistical power to detect the effect of bath and endotracheal suctioning and pressure injuries on some stress biomarkers. Additionally, because of sample size limitations and the use of linear mixed models, not all background characteristics such as sex, age and use of medication could be entered in multi-variable models. Since these factors did not appear to yield significant effects when testing bi-variable models, we chose to focus on the mediating effects of variables that showed statistical significance, such as pain and disease severity. Finally, due to the aforementioned limitations we chose to study only five biomarkers and two nursing interventions. Further study is needed to explore potential associations between additional critical care-related stressors and stress response markers.

It is noteworthy that we only observed significant associations between bed bath and serum neuropeptide levels, and not with endotracheal suctioning. Although endotracheal suctioning is among those procedures who have a higher risk for increased pain intensity (Puntillo et al., 2014) and it is a noxious and stressful experience (Puntillo et al., 2004; Puntillo et al., 2001), it did not seem to have a significant effect on stress neuropeptide levels in this investigation. Although this may in part be attributed to low statistical power and other confounders that could not be accounted for, it is worth considering whether the duration of the stimulus may also have a role in the modulation of stress neuropeptides. Typically, an endotracheal suctioning procedure lasts up to 15 seconds, which is much shorter compared to a bed bath lasting 15-20 minutes (El-Soussi & Asfour, 2017). Therefore, detection of a neuroendocrine response may be more likely with longer lasting stimuli.

In our study, prolactin and SP levels were significantly altered after bed bath, even when accounting for confounders. Although, associations between bed-bath and prolactin and SP have not been addressed before, it is worth comparing these results with those of studies on massage and touch since touch is a main component of bed-bath. In haematological oncology patients, Stringer et al. (2008) have demonstrated that massage reduced levels of prolactin, which is opposite to our findings. This discrepancy may be understandable based on differences in the properties of touch in the two studies. Although in massage, touch is intentionally relaxing, in bed-bath it can be mostly procedural and probably stressing. It is well established that prolactin is a stress-related biomarker, also associated with humiliating experiences (Lennartsson & Jonsdottir 2011; Sobrinho 2003). The administration of opiods can also stimulate secretion of prolactin (Vuong et al., 2010) and this is the reason why we adjusted our results for opioid administration.

The effects of bed-bath on SP are also noteworthy. SP is central in the transmission of noxious stimuli in the spinal cord (Gould & Kaye, 2012). Our results appear in line with those of Field et al. (2002) who observed a decrease in SP levels after massage therapy in fibromyalgia patients.

NPY is a multimodal molecule with orexigenic and metabolic effects, also involved in stress perception. NPY appears to mediate stress resilience and to have anxiolytic effects (Enman et al., 2015). Although no previous studies have addressed NPY modulation in patients with pressure injuries, our observation of increased NPY levels are in accordance with studies showing increased NPY in pain (Wang et al., 2014).

CONCLUSION

These novel results raise the possibility that nursing interventions and pressure injuries may modulate stress responses in critically patients. Therefore, nursing interventions and procedures, as well as wounds, need to be taken into account when evaluating the stress response in critical illness. More study is needed to elucidate the clinical significance of these findings. In the present study, bed bath appeared to have the most pronounced effect on stress neuropeptides. In the future, it would be worth exploring whether purposeful modifications in this procedure with the intent to maximize relaxation could have favorable effects on critically ill patients' stress biomarkers and outcomes.

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