A Preliminary Study: Neurological, Immunological, and Endocrine Aspects of Healthcare Workers without Burnout Syndrome

Yanuar Ardani[1,2,3], Hamzah Shatri[2,4], Sukamto Koesnoe[2,5], Em Yunir[2,6], Tjhin Wiguna[2,7], Heri Wibowo[2,8], Dian Ratna Sawitri[2,9], Sugeng Joko Sarwono[2,10], Muchtaruddin Mansyur[11], William Ricardo[3], Matilda Katarina[3], Rendi Faris Anggono[3]

[1]*Doctoral Program of Medical Science, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo National Hospital, Jakarta, Indonesia*
[2]*Lecturer of Doctoral Study, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo National Hospital, Jakarta, Indonesia*
[3]*Psychosomatic and Palliative Divison, Department of Internal Medicine, Faculty of Medicine. Diponegoro University. Kariadi General Hospital. Semarang Indonesia*
[4]*Psychosomatic and Palliative Divison, Departement of Internal Medicine, Faculty of Medicine University of Indonesia- Cipto Mangunkusumo National Hospital*
[5]*Allergy Immunology Division, Departement of Internal Medicine, Faculty of Medicine University of Indonesia- Cipto Mangunkusumo Hospital.*
[6]*Metabolic Endocrinology division, Departement of Internal Medicine, Faculty of Medicine University of Indonesia- Cipto Mangunkusumo Hospital.*
[7]*Departement of Psychiatry, Faculty of Medicine University of Indonesia- Cipto Mangunkusumo Hospital.*
[8]*Departement of Parasitology Pre-Clinic, Faculty of Medicine University of Indonesia- Cipto Mangunkusumo Hospital.*
[9]*Faculty of Psychology, Diponegoro University, Semarang, Indonesia*
[10]*Industrial Engineering Faculty. Bandung Institute of Technology. Bandung, Indonesia*
[11]*Department of Community Medicine Pre Clinic, Faculty of Medicine University of Indonesia- Cipto Mangunkusumo Hospital.*
Email: dr.yanuardani@gmail.com

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ABSTRACT
Summary: Healthcare workers are vulnerable to stress and burnout, which can affect the Hypothalamus-Hypophysis Axis (HHA) pathway. This pathway can involve psychological, neurological, immunological, and endocrine aspects. These can be evaluated using the Maslach Burnout Inventory Human Services Survey (MBI-HSS), a heart rate variability tool, laboratory tests using salivary immunoglobulin-A (sIg-A), T-cell regulator (TC), endorphins, and salivary cortisol (SC) levels.
Purpose: This study aimed to describe the neurological, immunological, and endocrine aspects of healthcare workers without burnout syndrome
Methods: A quantitative descriptive study was conducted to describe the psychological, neurological, immunological, and endocrine aspects of healthcare workers. Purposive sampling was used.
Findings: Sixty-two participants took the MBI-HSS, and 30 participants without burnout were selected. There were 28 nurses, with an average age of 28 years old. About 93,3% of the participants were female, 80% worked at the emergency department, and 60% had over three years of working experience. From HRV test results, 14 participants were within the normal range (50-100 ms). The average -endorphine serum level is 481,93 pg/ml. Around 60% of participants showed normal SC levels, and 40% showed low SC levels (mean 5,72 ng/ml). Around 90% showed normal sIg-A and 10% high sIg-A levels (mean 501,6 □g/ml). The average TC was 23% CD4, with 8,1% CD25 and 6,4% CD127.
Conclusion: This study found that average healthcare workers showed normal HRV, endorphins, SC, sIg-A, and T cell regulators, representing neurological, immunological, and endocrine aspects. Therefore, further study is needed to determine the impact of burnout syndrome on these aspects.

1. Introduction

Stress is a common phenomenon in everyday life. It involves a complex interaction between psychological and physiological responses that cannot be controlled consciously. Continuous, severe stress without adequate defense mechanisms can trigger burnout, characterized by physical and emotional exhaustion.[1] A study by Maslach et al. described burnout syndrome as a combination of emotional exhaustion, depersonalization, and low self-achievement caused by chronic stress. Prior studies have shown a relationship between burnout syndrome and errors at work, service satisfaction, and decreased professional work effort.[2]

The Maslach Burnout Inventory Human Service Survey (MBI-HSS) questionnaire is a scoring tool used to quantify burnout syndrome. The questionnaire assesses three dimensions of burnout syndrome: emotional exhaustion, depersonalization, and personal accomplishment. It also categorizes the severity of burnout

syndrome into not burnout, mild burnout, moderate burnout, and severe burnout.[3] Heri Yulianto has validated a Bahasa Indonesia version of the MBI-HSS.[4–6]

Neurological, immunological, and endocrine systems contribute to the human response to stress. Stress is known to activate the sympathetic nervous system, which triggers changes in peripheral adrenaline and noradrenaline secretion.[7] Noradrenaline will bring forth changes in heart rate, which could be assessed using Heart Rate Variability (HRV). HRV is the physiologic variation of heart rate intervals, which shows a complex interaction between the sympathetic and parasympathetic systems in the work of the sinus node.[8] A systematic review by Jarvelin et al. found that Burnout Syndrome was related to a decrease in HRV values mainly regulated by the vagal nerve.[9]

Severe stressors activate the hypothalamic-pituitary-adrenal axis (HPA axis), triggering the release of glucocorticoid hormones, which induce anti-inflammatory effects and immunosuppression. Prolonged activation of the HPA axis causes continuous high levels of circulating glucocorticoids, which can turn neurotoxic to the body and weaken the immune system.[7] A variable that can be measured is T-regulator cells, which control inflammation and immune tolerance by inhibiting proinflammatory cell responses and producing anti-inflammatory cytokines. Suppressed regulatory T cells can be found in individuals with chronic stress, such as burnout syndrome and depression.[10] Another biomarker for immune response is Imunoglobulin-A (IgA), which plays a vital role in mucosal immunity, allergic diseases, autoimmune diseases, and foreign proteins and has a concentration that can be affected by stress. IgA is found in the body's mucous membranes and bodily fluids, such as saliva.[11,12]

Several studies have shown a relationship between Burnout Syndrome and decreased responsiveness of the HPA pathway, which can cause hypocortisolism. Cortisol acts as a hormone that increases energy. High cortisol levels provide the ability to deal with stress. Hyperactivity of the HPA can change to hypoactivity if exposed to stress for an extended period without time for recovery.[13] Research by de Vente et al. shows that most studies link burnout to hypocortisolism, where there is a decrease in cortisol awakening response (CAR) levels.[14] In general, β-endorphin is a neurochemical involved in feelings of euphoria during exercise and is widely associated with emotions such as laughter, love, and appetite. Another effect of β-endorphin is immunosuppression by inhibiting splenocyte proliferation.[15] The study's primary purpose is to assess the impact of traditional music therapy on burnout syndrome among healthcare workers. It also aims to explore whether music therapy can effectively alleviate psychological and physiological stress, focusing on outcomes such as changes in burnout severity, heart rate variability (HRV), and biomarkers like cortisol and endorphins.

2. Research Design and Methods

This research is a qualitative and randomized control trial using a pre and post-test control group study design, Using cluster randomization to assess the impact of music therapy on burnout syndrome among healthcare workers., according to the inclusion and exclusion criteria.

Participants

Participants who fulfill the inclusion criteria listed below were recruited to the study:

1) Aged ≥ 18 years dan ≤ 60 years old,
2) Is a doctor or nurse working in Doctor Kariadi General Hospital Semarang,
3) MBI-HSS score < 44,
4) Is eligible for HRV examination

Subjects with chronic diseases, including cancer, thyroid diseases, cardiovascular diseases, untreated diabetes mellitus, and untreated hypertension, or who are on medications that affect the central nervous system, with psychiatric disorders, were pregnant, and did not like music, were excluded. The MINI-ICD 10 (Mini International Neuropsychiatric Interview) was used to screen for psychiatric disorders. Audiometry was done to screen for hearing impairments.

A total of 30 participants were included in this study.

Data Collection

Heart rate variability was assessed using the Max Pulse Medicare portable HRV device. During measurement, participants were required to keep their eyes open, sit still, and stay silent. If they had just done an activity, they

were required to rest for 10 minutes before measurement. Participants were also instructed to avoid taking deep breaths.

Blood samples were taken using a 3ml syringe and deposited into two tubes: the first tube containing ethylene diamine tetraacetic acid (EDTA) for hematology examination and the second without anticoagulant for ELISA testing.

Saliva sampling was done using the suction method. This involves allowing saliva to accumulate in the oral cavity for 30 seconds before being collected with a 0.5ml pipette. The sample is then stored in a tight plastic storage tube and sent for examination.

Serum cortisol was measured using the Human Cortisol ELISA kit available commercially (ElabScience) using blood samples. Using blood samples, beta-endorphin was measured using a commercially available Human-EP (Beta-Endorphin) ELISA kit (ElabScience). Serum IgA was measured using a Human IgA ELISA kit available commercially (ElabScience) using saliva samples.

All samplings were carried out on the 11th of November, 2023, at Doctor Kariadi General Hospital Semarang. Calcium, -endorphin, and IgA measurements were done in Universitas Diponegoro's GAKI Laboratory, while T-regulator cells were measured in Universitas Gajah Mada's Clinical Pathology lab.

Statistical Analysis

Descriptive data was presented in tabular form. Categorical data is reported as frequency (n) and proportion (%), while numerical data is reported as average (mean) and maximum and minimum values. Analysis was done using SPSS version 20.

3. Results

31 respondents met the study criteria, and one dropped out due to being sick. Hence, 30 participants were included in this study.

Table 1. Demographic Characteristics

No	Characteristics	Results (%)
1.	Gender	
	Male	2 (6.67%)
	Female	28 (93.33%)
2.	Age (years) Median	28
3.	Occupation	
	Nurse	28 (93.3%)
	Doctor	2 (6.67%)
4.	Last Education	
	Diploma	11 (36.67%)
	Bachelors	19 (63.33%)
5.	Working experience (years) Median	3 (1 – 15)

The subjects in this study were dominated by women (93,33%, n=28), and most worked as nurses (93,33%, n=28). The median age is 28, and the median working experience is three years, with one year being the shortest and 15 years being the most extended working period.

Table 2. HRV values

No	HRV	Results (Mean ± SD)
1.	SDNN (ms^2)	51,153 ± 19,90

For subjects without burnout syndrome, it was found that the mean SDNN was 51,153 ± 19,90 ms^2.

Table 3. Laboratory Results

No	Parameters	Results (Median)	Reference Value
1.	β-Endorphin (pg/mL)	503	319,5 - 643,2
2.	Cortisol (ng/mL)	5,55	3,4 - 8,52
3.	IgA (mg/mL)	0,44	0,33 - 0,63
4.	T-regulator cells FOXP3 event (%)	4	2 – 8

Laboratory results are shown in the table above (Table 3). Median salivary-endorphin levels were 503 pg/mL, within the average reference value of 15,625 – 1,000 pg/mL. The median salivary cortisol level was 5.55 ng/mL, within the average reference value of 5.0 – 21.6 ng/ml. Median salivary IgA levels were 0.44 mg/mL, within the average reference value of 0.05 – 0.49 mg/mL. Median FOXP3 levels were 4%, within the average 1.0 – 7.0% reference value.

4. Discussion

Demographic Characteristic

The study subjects were dominated by females, which may affect HRV and laboratory results. Prior studies have shown a higher sympathetic response in males, while females have a higher parasympathetic response. Another study showed higher HRV values for males than females.[16] The physiological functions of the body's endocrine are closely related, including sex hormones, such as androgens, estrogens, and progestins. Therefore, the endocrine system has evolved to respond to minimal changes in hormone levels; low changes in sex hormone levels cannot be ignored.[17] Current evidence supports the idea that sex chromosomes and gonadal hormones modulate the number and function of immune cells. There is strong evidence that type I and type II interferon signals and humoral responses are more significant in females than males. It is also implied that gender differences in innate and adaptive immunity contribute to the increased prevalence of autoimmunity in women and increase the likelihood of women experiencing post-transplant organ rejection.[18]

HRV

Higher HRV values imply better adaptability of the autonomic nervous system to stressors than those with lower HRV.[19] SDNN is an HRV component and the "gold standard" for predicting cardiac risk. SDNN values below 50ms are considered unhealthy, 50–100ms meaning impaired health, and above 100ms as healthy.[20] In this study, the average SDNN in healthcare workers without burnout syndrome was 51.15ms^2, implying preserved function of the autonomic nervous system against stressors. It should be noted that there is no standard for classifying SDNN values in healthy people, and HRV values may vary across age groups and genders.

Endocrine Aspects

This study found normal salivary β-endorphin and cortisol levels in healthcare workers without burnout syndrome, implying normal endocrine functions are retained in populations without burnout syndrome. In general, β-endorphin is a neurochemical involved in feelings of euphoria and is widely associated with positive emotions such as laughter, love, and appetite. The bond between β-endorphin and mu receptors in the central nervous system releases GABA inhibitors. It increases dopamine production, a neurotransmitter that is widely associated with feelings of pleasure and happiness.[15] Cortisol, the human primary stress hormone, targets peripheral systems and central processes. In addition to following a circadian or pulsatile rhythm, cortisol release is specific to stress. Stress refers to a situation in which demands are perceived to exceed a person’s resources. Most cells in the human body have receptors for cortisol, so cortisol has a wide range of effects throughout our systems, including metabolic, cardiovascular, and immune responses. Reactive stressors increase demands on the system through actual sensory stimuli, such as pain, bodily injury, or immune challenge. In contrast, anticipatory stressors tap into innate programs or memories, such as social challenges or unfamiliar situations.[21]

Immunological

A unique form of IgA, secretory IgA (s-IgA), is found in mucosal secretions, including saliva, which acts as a first-line barrier against invading pathogens. S-IgA is formed by two IgA molecules and a secretory component. S-IgA is under robust neuroendocrine control, especially the autonomic nerves innervating the salivary glands, strongly influencing s-IgA production. Thus, activation of the sympathetic nervous system increases the release of preformed IgA by plasma B cells and its epithelial translocation. However, under prolonged or chronic psychological stress, s-IgA response may be suppressed through various pathways, one of which is through the hormonal pathway, with cortisol as the primary stress modulator.[22] Measurement of salivary IgA levels in our study yielded expected results, which implies normal immune responses in healthcare workers without burnout syndrome.

Normal levels of FOXP3 were also found in subjects without burnout syndrome. Regulatory T cells play an essential role in the homeostasis of the immunological system. Regulatory T cells are formed by the transcription factor Forkhead box P3 (FoxP3) and the alpha chain of the IL-2 receptor (CD25). The primary role of regulatory T cells is to control inflammation and prevent the onset of autoimmune diseases. Depleting regulatory T cells in

individuals can cause a rapid inflammatory response, triggering autoimmune disease in multiple organs. An increase in the regulatory T set can cause a decrease in the cellular immune response and cause infection or abnormal cell growth. So, it is necessary to obtain a balance between regulatory T cells and effector T cells.[23,24]

ETHICAL CLEARANCE

This study was granted clearance from the Health Research Ethics Committee, Dr. Kariadi Hospital Semarang (Komite Etik Penelitian Kesehatan RSUP Dr. Kariadi Semarang), Number 1589/EC/KEPK-RSDK/2023. All subjects were provided with detailed information about the study and signed the informed consent form voluntarily. All subjects' information was kept confidential.

CONFLICT OF INTEREST

The authors declare that they have no competing financial or personal interests.

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AUTHOR CONTRIBUTION

All authors contributed equally to the manuscript's study, writing, and revision.

LIMITATION OF STUDY

There are some limitations in our research. This study involves mediators such as ACTH, POMC, and B cells beyond control, potentially affecting the results. Developing the music therapy model using the clinical expert judgment method may also introduce subjectivity. The short intervention period (4 weeks) with minimal dosage (1x/day, 3x/week) might be less effective in influencing endocrine and immunological aspects in individuals with burnout. Researching human subjects also presents challenges in controlling external stressors, such as increased workload and personal issues outside of work.

SUGGESTION

Traditional music therapy is recommended as a holistic, non-pharmacological treatment for burnout syndrome, with song selection tailored to patient preferences and PANAS testing before therapy. Further research is needed with medium to long-term interventions, increased therapy dosage, and combinations with psychotherapy or CBT to evaluate synergistic effects. Adapting traditional music arrangements should also consider sociocultural backgrounds to optimize its benefits.

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