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Cortisol level decreases natural killer cell activity among women exposed to aircraft noise

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ABSTRACT

One of the impacts of exposure to noise is stress. Natural killer (NK) cells are one of the leukocyte subsets that are responsive to physiological and psychological stress. The objective of the present research was to determine the relationship between cortisol levels and NK cell activity among women with aircraft noise stress in the area of Adi Sumarmo Airport, Solo**.** This study was an analytical survey with a cross sectional design. The number of subjects was 39, who were divided into 3 groups of 13 subjects each. Groups 1 to 3 were exposed to noise levels of 92.29 dB, 71.79 dB and 52.17 dB, respectively. The sample was taken using simple random sampling. The data were analyzed by Pearson correlation test and Anova followed by post hoc test using LSD test. The Anova test showed that there were significant differences in circulating cortisol levels among all groups ($p = 0.018$). The Pearson correlation test showed that there was a positive association between circulating cortisol levels and the number of NK cells ($r = 0.547$; $p< 0.05$) and a negative association between circulating cortisol levels and NK cell activity ($r = - 0.578$; $p < 0.05$). This study indicated that cortisol levels decreased NK cell activity among women with exposure to aircraft noise. Women who experienced aircraft noise stress showed increased cortisol levels and decreased NK cells activity.

Keywords : Aircraft noise, cortisol, natural killer cells, women

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INTRODUCTION

There is sufficient scientific evidence that noise has an influence on ischemic heart disease, hypertension, hearing impairment, sleep disturbance, and duodenal and gastric disorders. However, for other effects such as changes in the immune system, the evidence is limited.[1]

One of the impacts of exposure to noise is stress.[1-3] In response to a stressor, physiological changes are set into motion to help an individual cope with the stressor. However, a chronic activation of these stress responses, which include the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis, results in chronic production of glucocorticoid hormones and catecholamines.[3,4] Glucocorticoid receptors expressed on a variety of immune cells bind cortisol and interfere with the function of NF-kappa Beta (NF-KB), which regulates the

activity of cytokine producing immune cells. Adrenergic receptors bind epinephrine and norepinephrine and activated cAMP response element binding protein, inducing the transcription of genes encoding for a variety of cytokines. The changes in gene expression mediated by glucocorticoid hormones and catecholamines can dysregulate the immune system. Lymphocytes, natural killer cells, macrophages and granulocytes exhibit receptors for many neuroendocrine products of the HPA and SAM axes, such as cortisol and catecholamines which can cause changes in cellular trafficking, proliferation, cytokine secretion, antibody production and cytolytic activity.[5-7]

High intensity noise is more annoying than noise of low intensity, whilst intermittent noise is more annoying than continuous noise.[8] Women are more sensitive in response to noise than are men.[9] In the category of intermittent noise, aircraft noise is significantly more annoying. Chronic exposure to noise is thought to bring about significant impacts if it happens for more than a year.[1]

Natural Killer (NK) cells are important components of the innate immune systems, owing to their cytokine and chemokine production and ability to lyse target cells without prior sensitization. Human NK cells comprise ±15% of all lymphocytes and are defined phenotypically by their expression of CD56 and CD16, and lack of expression of CD3 ($CD56^+CD16^+CD3^-$).[10] Among the many indices of immune function, NK activity and NK cell subsets have been of interest to researchers because NK cells are known to be important in host defense against viral diseases and appear to play a significant role in protection against neoplastic growth.[11-13] NK cells are also one of the leukocyte subsets that are responsive to physiological stress and psychological stress.[14-16]

Based on the above considerations, the aim of this research study was to find out the presence of a correlation of circulating cortisol levels with NK cell numbers and NK cell activity among women with aircraft noise stress in the area of Adi Sumarmo Airport of Solo, Indonesia.

METHODS

Research design

This research study was an observational analytical study with cross sectional design. It was conducted from July 2008 to June 2009 among residents in the neighborhood of the runway of Adi Sumarmo International Airport of Solo, Indonesia, namely in the villages of Dibal and Gagak Sipat, Ngemplak subdistrict, Boyolali regency.

Subjects

The study population comprised all residents of Dibal village and Gagak Sipat village, Ngemplak subdistrict, Boyolali regency who fulfilled the following inclusion criteria: female, married, housewife, aged 20-40 years old (age influences the number of NK cells),[10] and having lived in the area for at least 1 year. Exclusion criteria were consumption of non-herbal or herbal medicines, pregnancy, hearing loss, infectious disease (colds, flu, and diarrhea), and diabetes mellitus.

The respondents who fulfilled the criteria were selected by means of simple random sampling. The sample size was calculated using the formula of Snedecor and Cochran or by using Win Episcope 2.0 with estimated difference between means (Ä = 0.05), for a confidence level of 95% and significance level of 5%. Based on the results of previous studies in the area,[17] the number of lymphocytes S_D was 700; m_1 was 3.6 x 10^3/µl; m_2 was 2.5 x 10^3/µl, and the number of subjects per group was 13. The total number of subjects was 39, who were divided into 3 groups, on the basis of the distance of their residential area from the runway. Group 1 respondents lived at a distance of less than 500 meters from the tip of the runway; group 2 respondents were

subjects whose residential area was between 500 and 1,000 meters from the tip of the runway, while group 3 respondents lived at a distance of more than 1,000 meters from the tip of the runway.

The subdivision into groups according to the distance of their residence to the runway was based on the following considerations:

1. Previous research by Hartono[17] in the same geographical area showed that at a distance of less than 500 meters from the runway, the noise intensity was 96.57 dB, as measured with the WECPNL scale. At a distance of more than 1000 meters from the runway, the noise intensity was 51.56 dB on the WECPNL scale, while at a distance of 500 to 1000 meters from the runway, the noise intensity was 74. 42 dB measured with the WECPNL scale.[18]
2. The area around the airport with a noise intensity level of more than 80 dB WECPNL is not recommended for settlement and was therefore chosen as the exposure area, whereas the area with a noise intensity level of less than 56 dB WECPNL was used as the control area, since the area is safe for settlement (Decree of Director General of Air Transportation No. SKEP/109/VI, for the year 2000).

Measurement of noise exposure

The noise exposure was measured using a sound level meter (Extech Model 407735, Japan) and rated according to WECPNL. In each of the two study areas measurement of noise was conducted at three different points with a portable sound level meter (SLM), and the acoustic physical parameter was measured in dB with A load. The SLM was placed with its filter parallel to the subject's ears. The SLM was set up at its maximum function of value to measure the peak noise level of aircraft passing over the areas so that the background noise level could be blocked. The acoustic physical parameter was recorded based on the peak noise level occurring at aircraft take-off and landing, and the time of occurrence of noise level was also recorded. The noise level was rated by using the WECPNL (Weighted Equivalent Continuous Perceived Noise Level) scale, according to the following equation:

$$\text{WECPNL} = \text{dB (A)} + 10 \log N - 27$$

$$N = N_1 + 3N_2 + 10N_3$$

dB (A): Average decibel score of each peak level of aircraft activity in a day.

N : Number of aircraft arrivals and departures in 24 hours.

N_1 : Number of aircraft arrivals and departures between 07.00 and 19.00 Western Indonesia Time

N_2: Number of aircraft arrivals and departures between 19.00 and 22.00 Western Indonesia Time

N_3: Number of aircraft arrivals and departures between 22.00 and 07.00 Western Indonesia Time

The measurements in dB (A) were then converted into WECPNL in accordance with the number of aircraft passing over the area in 24 hours.

Biochemical measurements

After the subjects had been selected, 4 mL of venous whole blood was taken from the respondents, between 7.00 to 08.00 Western Indonesian Time. Subsequently the plasma cortisol level was measured by means of enzyme-linked immunosorbent assay (ELISA). The number of NK cells was determined as follows: peripheral blood mononuclear cells (PBMC) were separated from 10 mL of the whole blood using Ficoll-Hypaque density-gradient centrifugation (30 minutes, 20^{o}C, 400 x g). The PBMC were washed twice with PBS and suspended in RPMI 1640 medium (Gibco,

Invitrogen) containing 10% (vol/vol) fetal bovine serum, penicillin (100 IU/mL) and streptomycin (100 µg/mL), stored at 4°C until required for analysis. NK cells were enumerated by three-color immunophenotyping using appropriate combinations of monoclonal antibodies (PharMingen, San Diego, CA), these being conjugated fluorescein isothiocyanate (FITC), phycoerythrin (PE) and perpridinin-chlorophyll protein (PerCP). Briefly, a sample of 1 x 10^6 PBMC was mixed with saturating amounts of monoclonal antibody conjugated with FITC (anti-CD16), PE (anti-CD56) and PerCP (anti-CD3). After being washed twice with PBS, the stained cells were passed through a FACScan flow-cytometer (Becton Dickinson). The number of NK cells in PBMC was calculated as a percentage of $CD16^+CD56^+CD3^-$ cells.[13,14,16]

NK cell activity was measured by a non-radioactive method, which was a modification of the procedure conducted by Andalib et al.[19] The lymphocytes were separated by means of the Ficoll-Hypaque gradient technique (Lymphoprep, Norway). Lymphocytes were isolated, washed, and brought to a concentration of 5 x 10^5 cells/mL in RPMI 1640 + 10% FCS (Gibco, Germany).

ATCC-K562 erythromyelocytic leukemia cells as the target cells were maintained in continuous suspension culture in RPMI 1640 + 10% FCS, supplemented with L-glutamine, 100 µg/mL streptomycin and 100 U/mL penicillin. A working solution was prepared by adding 0.5 µg/mL propidium iodide (PI, Sigma) in RPMI 1640 + 10% FCS. The lymphocytes (effectors) and K562 leukemia cells (target cells) were mixed and cultured in the same tube, with a target to effector ratio of 50:1. Briefly, the tubes containing the mixed cells were centrifuged for 7 minutes at 250 x g at room temperature, then kept at 37°C for 10 minutes in a water bath, after which the mixed cells were resuspended.

In the working solution, a concentration of 1 x 10^5 cells/mL was prepared to avoid recycling of NK cells. The samples were then incubated for 1.5 hours at 37°C, under 5% CO_2, then the cell concentration brought to 1 x 10^6 cells/mL and the samples were ready for flow-cytometry. The resulting measurements were read twice by two different observers. To monitor the spontaneous death rate of NK cells, target cells only (without effector cells) were incubated. The final concentration of 1 x 10^5 cells/mL has been running as control. The cells were analyzed with a FACSCalibur flow cytometer (Becton Dickinson, Palo Alto, CA, USA). NK cell activity was calculated based on the percentage of dead target cells (K562) in the tube containing effector cells, subtracted by the percentage of dead target cells in the control tube (without effector cells), divided by the total number of cells (100%), and subtracted by the dead target cells in the control tube (without effector cells), as shown in Figures 1-3.

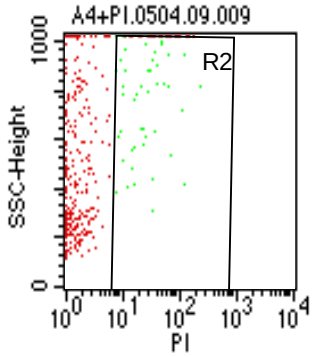

Figure 1. Comparison between living K562 target cells, labeled in red color, and dead target cells, labeled in green color, in group 1

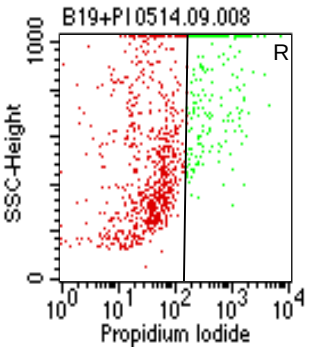

Figure 2. Comparison between living K562 target cells, labeled in red color, and dead target cells, labeled in green color, in group 2

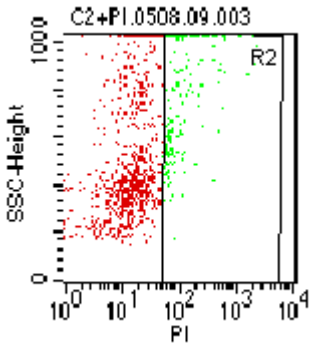

Figure 3. Comparison between living K562 target cells, labeled in red color, and dead target cells, labeled in green color, in group 3.

The dot plot has been defined as fluorescence light-2 (SSC-Height) versus fluorescence light-1 (PI) detectors that show the fluorescence intensity in distinctive stained cell populations (i.e. gated specific populations). Dead K562 cells form a well-defined population with distinctive fluorescence staining with propidium iodide (green gated). The dot-plot is illustrated the representative for dead (green) and live target cell population (red) based on propidium iodide dye staining, in comparison with control cells (red population only) for K562. The calculation of cytotoxicity is based on the two different gated cells with the proportion of cell population based on the acquisition data on system.

Data analysis

The study data were analyzed by analysis of variance (Anova) to verify the differences in cortisol level, number of NK cells, and NK cell activity, among the three groups of respondents. Pearson's product moment correlation test was used to investigate the correlation of cortisol level with number of NK cells and activity of NK cells.

Ethical clearance

The study participants were subject to the ethical clearance-related measures and procedures. Ethical clearance was obtained from the Ethical Review Committee, School of Medicine, Sebelas Maret University. The research study was also subject to confidentiality and anonymity principles towards the data on the respondents.

RESULTS

The data on noise intensity level (WECPNL), cortisol level, NK cell numbers and activity for each group are presented in Table 1.

The study showed that at a distance of less than 500 meters from the runway, the noise intensity was 92.29 dB, while at a distance of 500 to 1,000 meters from the runway the noise intensity was 71.49 dB, and at a distance of more than 1,000 meters from the runway the

Table 1. Noise intensity level (WECPNL), circulating cortisol level, and number and activity of NK cells in each group

Variables	Group 1 (n=13)	Group 2 (n=13)	Group 3 (n=13)	p value
Noise intensity level (dB)	92.29	71.49	52.17	
Cortisol level (µg/dl)	13.25 ± 3.06 [a]	12.19 ± 3.53 [b]	10.15 ± 2.42 [c]	0.018
Number of NK cells (%)	18.80± 6.85 [a]	17.52 ± 5.62 [a]	12.88 ± 5.17 [b]	0.038
Activity of NK cells (%)	12.50 ± 3.25 [a]	17.20 ± 3.06 [b]	22.33 ± 6.30 [c]	0.000

[a, b, c] real difference in post hoc test using LSD test completed with homogenous subsets with á = 0.05.

Notes:

Group 1, respondents residing less than 500 meters from tip of runway at noise intensity of 92.29 dB
Group 2, respondents residing between 500 and 1,000 meters from tip of runway at noise intensity of 71.79 dB
Group 3, respondents residing more than 1,000 meters from tip of runway at noise intensity of 52.17 dB

Table 2. Pearson's correlation coefficient between cortisol level and number and activity of NK cells

Variables	Cortisol	NK cell activity	NK cell numbers
Cortisol	1	- 0.578*	0.547*
NK cell activity	- 0.578*	1	-0.343
NK cell numbers	0.547*	-0.343	1

noise intensity was 52.17 dB, all dB measurements being on the WECPNL scale.

The mean cortisol levels of the respondents in areas 1, 2, and 3, were 13.25 µg/dl, 12.19 µg/dl, and 10.16 µg/dl respectively, which were significantly different (p=0.018). Follow up with the post hoc test (á =0.05) showed that there was a significant difference between cortisol levels in the different groups, with the highest levels in area 1 and the lowest in area 3 ($p<0.05$).

Based on Table 1, it can be seen that the mean numbers of NK cells ($CD56^+CD16^+CD3$) of the respondents in groups 1, 2, and 3 were 18.80%, 17.52%, and 12.88% respectively. These results were significantly different (p=0.038) and follow up with the post hoc test (á=0.05) showed that there was a significant difference between NK numbers in the different groups of respondents ($p<0.05$).

The activity of NK cells of the respondents of groups 1, 2, and 3 were 12.50%, 17.20%, and 22.33% respectively. The results of the Anova test showed that there was a significant difference in the mean activity of NK cells among the three groups (p=0.000). After the Anova test was continued with the post hoc test, the results were similar to those on cortisol level. There was a significant difference in mean activity of NK cells between group 1 and group 3, between group 1 and group 2, and between group 2 and group 3 ($p<0.05$).

The results of Pearson's product moment correlation test showed that there was a significant positive correlation between circulating cortisol levels with the number of NK cells ($CD56^+CD16^+CD3^-$) [$r=0.547$; $p<0.05$] (Table 2) and a negative (or inverse) correlation between circulating cortisol levels and NK cell activity ($r=–0.578$; $p<0.05$), signifying that cortisol level is inversely proportional to NK cell activity. The increase in NK cell numbers due to noise exposure had a negative correlation with NK cell activity, but the correlation was less strong (r=-0.343 and $p<0.05$) (Table 2).

DISCUSSION

From the test results we can conclude that exposure to aircraft noise at an intensity level of 71.49 dB (WECPNL) for more than one year acted as a stressor which increased the mean cortisol level of the treatment groups compared to that of the control group (intensity level of 52.17 dB). In the group with aircraft noise at an intensity level of 92.29 dB (WECPNL) the noise acted as a stressor, resulting in a higher increase in mean cortisol level than was the case with aircraft noise at an intensity level of 71.49 dB (WECPNL).

The aforementioned results are similar to those reported by Cheng and Ariizumi (2007) who did an experiment with BALB/c mice at a noise intensity level of 90 dB, with a length of exposure of five hours per day for four weeks. The mean cortisol level of the treatment group of mice exposed to noise for four weeks was 4.25 µg/dl, which was higher than that of the control group, with mean cortisol level of 1.60 µg/dl.[20] This is in line with the results of a research study conducted by Dhanalakshmi et al., who reported that cold stress applied to

white rats resulted in increased plasma cortisol levels, which affected their immune system.[21]

It is known that continuous recurrent aircraft noise will bring about stress. This chronic stress will increase the cortisol and catecholamine levels through HPA and SAM pathways.[6,11,22] The increase in cortisol level via the glucocorticoid receptors will inhibit production of several cytokines generated by NK cells (IFN-á, IFN-â, IFN-ã, IL-10, GM-CSF, and TNF-â). Interferon is a major regulator of NK cells.[6,10] IFN-ã functions to inhibit the proliferation of NK cells through the inhibition of IL-4, thus decreased INF-ã production will cause increased proliferation of NK cells. [10,23,24]

The role of IL-2 is to increase the proliferation of NK cells through the interleukin-2 receptors (IL-2Ráâã) which are expressed by NK cells of $CD56^{bright}$ and IL-2Ráâã receptors which are expressed by NK cells of $CD56^{dim}$. In relation to the proliferative response, the two receptors have a high proliferation response toward IL-2 at a low dosage and do not have any responses if both receive a high dosage of IL-2, particularly IL-2Ráâã. The decreased level of IL-2 (low-dosage) due to the inhibition of glucocorticoid activity will result in increased proliferation of NK cells.[10,24]

Several findings of animal model studies show that the increase in glucocorticoids due to stress in the long term resulted in a decreased activity of NK cells.[6,25,26] The activity of NK cells is influenced by TNF and the interferons (IFN á, â, and ã), which cause an increase in the cytolytic function of NK cells. IFN-á brings about a higher increase to the cytolytic functions than IFN-ã. Other lymphokines also have effects on NK cells. IL-12 and IL-2 synergistically increase the cytotoxicity of NK cells. NK cells are also able to lyse cells with the aid of IL-2. On the one hand IL-2 is potent induction factor for cytokine production by NK cells. On the other hand, IL-2 is also a growth factor for NK cells and plays a role in increasing the cytotoxicity and migration of NK cells.[10,12,27]

The increase in cortisol level due to stress in the long term will inhibit the activity of NF-êB (NF-kappa Beta). Due to such inhibition, several cytokines generated by NK cells (IFN-á, IFN-â, IFN-ã, IL-10, GM-CSF, and TNF-â) and IL-2 and IL-4 generated by T cells will decrease in terms of their production. The decrease in the levels of cytokines TNF, IFN, IL-2 and IL-12, which is caused by inhibition of cortisol activity, will cause a decrease in NK cell activity.[10,12,23]

These results are similar to those reported by Andalib et al. in a study on 45 women suffering from chronic stress due to recurrent spontaneous abortion.[19] Their study showed that there was a high level of stress in women with recurrent spontaneous abortion, and such a stress condition resulted in decreased activity of NK cells. Similar results were also reported by Morikawa et al., Suzui et al. and Nagao et al.[13,14,16]

CONCLUSION

There was a relationship of circulating cortisol levels with natural killer cell activity and numbers among women with aircraft noise stress in the area of Adi Sumarmo Airport, Solo, Boyolali. Based on the results of the study, preventive measures are needed to deal with the aircraft noise to prevent further negative impacts on residents around Adi Sumarmo International Airport, Solo, Boyolali.

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