



Original Article

Effect of music therapy on cortisol as a stress biomarker in children undergoing IV-line insertion

Idyatul Hasanah, MN^{a,*}, Sri Mulatsih, Ph.D^b, Fitri Haryanti, Ph.D^c and Zikrul Haikal, MD^d

^a Department of Nursing, Mataram Institute of Health Science, Mataram, Indonesia

^b Department of Hematology and Oncology Paediatrics, Paediatric Department, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia

^c Department of Paediatric Nursing, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia

^d Faculty of Medicine, Universitas Mataram, Mataram, Indonesia

Received 24 January 2020; revised 11 March 2020; accepted 15 March 2020; Available online 14 April 2020



المخلص

أهداف البحث: غالبا ما يؤدي غرز الخط الوريدي إلى إحداث ضغط عصبي يمكن أن يؤدي إلى ارتفاع في مستويات الكورتيزول. هناك حاجة إلى العلاج التكميلي مثل العلاج بالموسيقى للتغلب على ارتفاع مستويات الكورتيزول. أجرينا هذه الدراسة لتحديد تأثير العلاج بالموسيقى على مستويات الكورتيزول في اللعب لدى الأطفال المصابين بسرطان الدم الخاضعين لغرز الخط الوريدي.

طرق البحث: هذه دراسة تجريبية مع تصميم اختبار قبلي وبعدي. تم تحليل مستويات الكورتيزول في اللعب عند ٣٠ طفلا مصابين بسرطان الدم خاضعين لغرز الخط الوريدي من يناير إلى فبراير ٢٠١٨. تم تشغيل الموسيقى باستخدام سماعات الأذن بعد إكمال إجراء غرز الخط الوريدي. كما تم تحليل مستويات الكورتيزول في اللعب باستخدام اختبار إليسا. وتم اعتبار التغيرات في مستويات الكورتيزول مهمة سريريا إذا كان الفرق ≤ 0.05 نانوجرام/مل. وتم استخدام اختبار ويلكوكسون لفحص تأثير العلاج بالموسيقى على مستويات الكورتيزول.

النتائج: كان لمستويات الكورتيزول قبل وبعد العلاج بالموسيقى متوسط (الأدنى –الأقصى) ٤.١٤ (٠.٢٥-٩.٨٩) و٣.٤٧ (٠.١٦-١٥.٣١)، على التوالي. وكان الاختلاف المتوسط لمستويات الكورتيزول ٠.٦٧ نانوجرام/مل. يشير هذا التغيير ≤ 0.05 نانوجرام/مل إلى التأثير السريري للعلاج بالموسيقى على مستويات الكورتيزول. بالرغم أن العلاج بالموسيقى لم يكن له تأثير كبير على مستويات

الكورتيزول في اللعب، ولكن أظهرت هذه الدراسة التأثير السريري للعلاج بالموسيقى في خفض مستويات الكورتيزول.

الاستنتاجات: لم تظهر هذه الدراسة تأثيرا ذا دلالة إحصائية للعلاج بالموسيقى على مستويات الكورتيزول عند الأطفال المصابين بسرطان الدم أثناء غرز الخط الوريدي. ولكن، نتائج الدراسة تعكس التأثير السريري للعلاج بالموسيقى في خفض مستويات الكورتيزول.

الكلمات المفتاحية: العلاج بالموسيقى؛ الكورتيزول؛ الضغط العصبي؛ سرطان الدم

Abstract

Objective: An IV-line insertion can often provoke stress that can lead to an increase in cortisol levels. Complementary medication such as music therapy is needed to overcome the increase in cortisol levels. We conducted this study to determine the effect of music therapy on salivary cortisol levels in children with leukaemia undergoing IV-line insertion.

Method: This was a pre-experimental study with a pre-and post-test design. We analysed the salivary cortisol levels in 30 children with leukaemia undergoing IV-Line insertion from January until February 2018. Music was played using earphones after the completion of the IV-line insertion procedure. The salivary cortisol levels were analysed by an enzyme-linked immunosorbent assay (ELISA) test. Changes in cortisol levels were considered clinically significant if the differences were ≥ 0.05 ng/ml. The Wilcoxon test was used to test the effect of music

* Corresponding author. Department of Nursing, Mataram Institute of Health Science, Jl. Swakarsa 3 No.18, Kekalik Jaya, Sekarbela, Nusa Tenggara Barat, Mataram, Indonesia.

E-mail: idyatulhasanah@gmail.com (I. Hasanah)

Peer review under responsibility of Taibah University.



therapy on cortisol levels and a p -value of <0.05 was considered statistically significant.

Result: Levels of cortisol before and after the music therapy had a median (min–max) of 4.14 (0.25–9.89) and 3.47 (0.16–15.31), respectively. The median difference of cortisol levels was 0.67 ng/ml. This change of ≥ 0.05 ng/ml indicates the clinical effect of music therapy on cortisol levels. Though the music therapy did not significantly affect salivary cortisol levels ($p = 0.99$), this study revealed the clinical effect of music therapy in reducing cortisol levels.

Conclusions: This study did not indicate a statistically significant effect of music therapy on cortisol levels of children with leukaemia during an IV-line insertion. However, the study findings reflect the clinical effect of music therapy in reducing cortisol levels.

Keywords: Cortisol; Leukaemia; Music therapy; Stress

© 2020 The Authors.

Production and hosting by Elsevier Ltd on behalf of Taibah University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Global Burden of Cancer in 2015 reported that leukaemia is a type of cancer with the highest incidence in children.^{1,2} In 2013, there were 414,000 new cases of leukaemia worldwide and the mortality rate reached 265,000.² Childhood leukaemia is a major threat to public health worldwide including developing countries such as Indonesia. In Yogyakarta, the leukaemia incidence has increased annually.^{3,4}

Children with leukaemia will undergo a longer treatment procedure lasting about two or two and a half years^{5,6} and a series of invasive procedures such as repeated venous access.⁷ In developed countries, to facilitate venous access in patients with leukaemia and for those who receive a chemotherapy procedure, the tool called ‘*port a cath*’ is used. This tool enables the health workers to administer chemotherapy, fluids access, and medicines, take blood samples, and give nutrients without making the recurrent IV-line insertion. In Indonesia, this tool is rarely used. Children need to undergo recurrent venous access that causes a stressful condition.^{6,8,9} One of the stress responses, when children take the IV-line insertion procedure, is the change in cortisol level.^{10–14} Cortisol is considered the biochemical marker for both acute and chronic stress.^{13–18}

In general, children are not able to express their stress conditions, so the stress condition inspection method using salivary cortisol is perceived to be more beneficial. Salivary cortisol is a better, more effective and a valid method of examination compared to blood tests in assessing adrenocortical function, additionally, it is easier to collect, non-invasive, fast, and can be repeated.^{13,15,17,19}

This study is important because stress conditions due to exposure to pain when the child undergoes an IV-line

insertion can cause a child to develop a fear and avoid the medical procedures so that it can indirectly have an impact on the quality of life, increasing morbidity and mortality.¹¹ One of the complementary approaches to manage child stress is music therapy.^{20–25} It is considered feasible, easy and cost-effective.^{26–28} Identification of stress conditions using salivary cortisol when the child is undergoing IV-line insertion can be a reference for health workers in providing quick and appropriate action to reduce stress. This study aims to examine the effect of music therapy on salivary cortisol levels as a stress biomarker in children with leukaemia who are undergoing an IV-line insertion.

Materials and Methods

Participants and sample size

The subjects are children with leukaemia in the *Paediatric One Day Care* and *Estella* (paediatric cancer) ward of Dr Sardjito General Hospital, Yogyakarta, from January until February 2018. Dr Sardjito General Hospital, Yogyakarta, is a national referral hospital that has an integrated cancer centre. The sample criteria are children with leukaemia who undergo an IV-line insertion, aged 6–18 years old, have no hearing problems, like to listen to music, have not eaten, or drank 30 min prior to the saliva sampling, and the parents’ consent for their children becoming respondents. All children who met the inclusion criteria participated in the study. This study has $\alpha < 0.05$, 95% CI, and research power is 80%. The sample size was determined based on previous studies using large numerical analytic sample formulations in pairs with repeated measurements of more than twice the measurements. The biggest calculation result is 28 respondents with a drop out calculation of 10%, and the minimum sample sizes that must be met in this study are 30.

Instrument

The protocol of music therapy is based on the guidelines of music therapy designed by Robb et al.²⁹ The music therapy used is based on patient preferences, and is administered for 20 min and it is provided through an MP3 player using earphones.^{20,30} The saliva samples were measured using the ELISA kit 96 wells DES661. The determination of the sample concentration is done by comparing the sample absorbance value with the standard absorbance.³¹

Design and procedure

This was a pre-experimental study with one group pre-test and post-test design. The study was conducted after the approval by the Ethics Committee of Gadjah Mada University and was allowed by the authorities involved with the supervision of the research site. The researchers took saliva samples, while the measurement of salivary cortisol levels was conducted in the Clinical Pathology laboratory, Faculty of Medicine Gadjah Mada University. This study process can be explained in three stages:

1. Pre-intervention Stage

The medical records were reviewed to determine the characteristics of the respondents such as names, ages, genders, drug consumed, comorbidities (i.e. fever, anaemia, sepsis, Bell's palsy or other comorbidities), and needle insertion frequencies. In this stage, we conducted a screening for emergency conditions, hearing functions, musical fondness, and last meal/drink. The first salivary sampling was taken in the 20 min after IV-line insertion or before the music therapy is given.

2. Intervention Stage

In this stage, the subjects were given music therapy. Music was played just after the first salivary sampling, for 20 min in a single session, using earphones.

3. Post-Intervention Stage

The last salivary sampling was taken after the music session.

Data analysis

The effect of music therapy on salivary cortisol levels was determined by testing the difference in the mean of salivary cortisol levels by comparing the measurements before and after the music therapy. Before testing the effect of music therapy on cortisol levels, we first tested the differences in variables suspected to influence salivary cortisol levels to ensure that the cortisol level change is caused by music therapy. External variables in this study that affect cortisol levels include age, sex, comorbidities, drug consumption, and frequency of needle insertion.

The data on the respondent's characteristics were analysed by univariate analysis. Categorical data was presented in the frequency table (n) and as a percentage (%). Clinically,

the cut-off point for an increase or decrease in cortisol levels that are considered significant is if a difference of ≥ 0.05 ng/ml is obtained.³² Statistically, the effect of an external variable on salivary cortisol level is analysed using the Mann Whitney test and Kruskal Wallis test. The Wilcoxon test is used to determine the effect of music therapy on cortisol levels. The study used $\alpha < 0.05$, 95% Confidence Interval (CI), research power was 80%, and p-value < 0.05 considered significant. Data were analysed using IBM SPSS version 24 for Windows.

Results

The inclusion criteria were met by 34 respondents. Four respondents were excluded because two respondents asked to stop listening to music early, one respondent stopped listening to music as they had to undergo intrathecal chemotherapy, and one respondent had an error during the cortisol examination. The respondent's characteristics and the effect of an external variable on salivary cortisol levels are presented in [Tables 1 and 2](#).

Only variables of comorbidities have p-value < 0.05 which means that comorbidities affect the changes in cortisol levels ([Table 2](#)). Thus, it can be concluded that changes in cortisol levels that occurred were not caused by music therapy but were also influenced by comorbidities suffered by the respondents. The effect of music therapy on salivary cortisol levels was determined by testing the difference in the median of salivary cortisol levels by comparing the measurement results before and after the music therapy ([Table 3](#)).

The median difference before and after music therapy was 0.67 ng/ml, confirming that the value of the difference between the two measurements was ≥ 0.05 ng/ml ([Table 3](#)). This indicated that clinically the music therapy helped to reduce salivary cortisol levels. The Wilcoxon test presented a p-value of 0,99 ($p > 0.05$) indicating that there was no significant difference between salivary cortisol levels before

Table 1: Respondent's Characteristics.

| Variable | Characteristics | (n = 30) | Percentage (%) |
|------------------------------|-----------------------------|----------|----------------|
| Age (years) | Child ^{6–12} | 23 | 76,7 |
| | Adolescent ^{13–18} | 7 | 23,3 |
| Sex | Male | 20 | 66,7 |
| | Female | 10 | 33,3 |
| Drugs consumed | Yes | 26 | 86,7 |
| | No | 4 | 13,3 |
| Comorbidities | Yes | | |
| | Anaemia | 18 | 60,0 |
| | Bell's palsy | 1 | 3,3 |
| | Fever | 1 | 3,3 |
| | Sepsis | 1 | 3,3 |
| | No | 9 | 30 |
| Needle insertion frequencies | 1 | 24 | 80 |
| | 2 | 4 | 13,3 |
| | 3 | 0 | 0,0 |
| | 4 | 2 | 6,7 |

Table 2: The effect of external variables on salivary cortisol levels.

| Variable n ³⁰ | Cortisol levels | | Differences | p-value |
|--------------------------------------|-------------------|-------------------|-------------------|---------------------|
| | Before | After | | |
| | Median (min–max) | Median (min–max) | | |
| Age | | | | |
| Children ²³ | 4,61 (0,25–9,89) | 4,48 (0,25–15,31) | –0,00 (9,35–3,18) | 0,17 ^a |
| Adolescent ⁷ | 3,80 (0,35–7,28) | 3,33 (0,16–6,16) | –0,54 (2,47–3,95) | |
| Sex | | | | |
| Male ²⁰ | 6,02 (0,26–9,89) | 4,48 (0,26–6,16) | –0,00 (9,35–3,18) | 0,56 ^a |
| Female ¹⁰ | 2,19 (0,25–7,28) | 1,89 (0,16–8,37) | –0,03 (5,72–3,92) | |
| Drugs consume | | | | |
| Yes ²⁶ | 3,46 (0,25–9,68) | 3,27 (0,16–15,31) | –0,00 (9,35–3,95) | 0,62 ^a |
| No ⁴ | 6,21 (4,61–9,89) | 6,08 (2,69–10,35) | –0,14 (0,47–1,92) | |
| Comorbidities | | | | |
| Yes ²¹ | 4,17 (0,258–9,89) | 4,48 (0,16–15,31) | 0,20 (9,35–1,92) | 0,01 ^{*.a} |
| No ⁹ | 4,12 (0,61–8,02) | 3,16 (0,44–7,38) | –0,63 (0,99–3,95) | |
| Frequency of needle insertion | | | | |
| 1 ²⁴ | 4,97 (0,25–9,89) | 4,00 (0,25–15,31) | –0,00 (9,35–3,95) | 0,70 ^b |
| 2 ⁴ | 1,80 (0,61–3,68) | 1,89 (0,44–6,16) | 0,08 (2,47–0,17) | |
| 4 ² | 5,01 (0,35–9,68) | 5,35 (0,16–10,54) | 0,34 (0,86–0,19) | |

Note: min: minimum; max: maximum; (*) p-value <0.05 is significant; (^a) analysed by Mann Whitney test, (^b) analysed by Kruskal Wallis test.

Table 3: Effect of music therapy on salivary cortisol levels.

| Cortisol ng/ml | Mean differences | |
|----------------------|-------------------|---------------------|
| | Median (min-max) | p-value |
| Before music therapy | 4.14 (0.25–9.89) | 0.99 ^{*.a} |
| After music therapy | 3.47 (0.16–15.31) | |

Min: minimal value, Max: maximal value, *: p-value > 0.05 no effect, ^a: analysis by Wilcoxon signed-rank test.

and after the music therapy. This means that, statistically, the music therapy did not affect cortisol levels.

Discussion

The study began after patients underwent the IV-line insertions. The first sample is taken about 20 min after the IV-line insertion because the peak increase in cortisol levels occurs around 20–40 min after exposure to stress and can be used as evidence of body response to stress.^{12,13} The hope, when there is a high increase in cortisol that the effect of music therapy helps in reducing cortisol can be seen more clearly.

Changes in cortisol levels that occur are not caused by music therapy but also by other variables such as comorbidities. Comorbidities suffered by patients include fever, anaemia, sepsis, and Bell's palsy. *Cortisol Binding Globulin* (CBG) as a cortisol binding protein is a thermocouple protein, a protein that is sensitive to temperature changes and releases cortisol in response to fever.³³ Cortisol increases occur with the increase of *C-Reactive Protein* (CRP) and *procalcitonin* (PCT) in patients with sepsis.³⁴ Two children in this study were also diagnosed with Bell's palsy and sepsis. One child had a defect in the facial area around the nose and mouth. Increased levels of high cortisol are associated with the disability they suffered.³⁵

Statistically, music therapy had no significant effect on salivary cortisol levels (Table 3). Music therapy does not affect cortisol levels in response to stress.^{36,37} The insignificance of statistical analysis can be caused by several things, including a very wide measurement range of cortisol levels in some patients, homogeneity of the clinical conditions and the level of stress exposure, environmental factors, and time and duration of the music therapy.

A wide range of cortisol levels is caused by several patients displaying extreme cortisol levels after listening to music. Increased cortisol levels may be caused by several conditions during the study, such as patients receiving intravenous drugs while the music therapy is in progress, having a defect around the mouth and nose so it is difficult to collect saliva samples, intravenous needle insertion up to four times, and unintentional needle removal, all patients who had a relapse after one and a half years of free treatment, and situations where mothers who cried while sitting beside her child during the music therapy session. The symptoms and stress levels of a person are closely related to the degree of physical suffering.³⁸ The increase in cortisol is generally proportional to the intensity and magnitude of stress stimuli. A greater increase in cortisol levels is generated in response to severe stress.¹⁰ Music therapy is a complementary therapy that can be used to reduce stress response, but in the above conditions, music therapy cannot stand alone or be given as a single stress therapy. The provision of singular music therapy in individuals with highly increased levels of cortisol may have a minimal effect and even no effect at all.

Homogeneity of the clinical conditions and level of stress exposure during the study was difficult to control, for example, medical procedures are undertaken, drugs are consumed, the severity of the disease, frequency of needle insertion, and the level of physical suffering. This can affect the level of stress in children and adolescents with cancer.³⁹ Music cannot alleviate the symptoms of stress but can

aggravate the condition in cancer patients.⁴⁰ The uncontrollable environmental disturbances while the music therapy is in progress such as some patients near him running around, talking, crying, or shouting. It is common knowledge that most of the respondents share a room consisting of 16 beds that are separated only by a curtain, hence the music therapy is not optimised. Environmental noise may interfere with the effectiveness of music therapy even when using earphones.^{20,37}

The timing and duration of music therapy may also have an impact. Most of the patients in this study received music therapy before undergoing other medical interventions such as intrathecal chemotherapy or BMP. This can result in the child experiencing greater anxiety so that the effects of music therapy is minimised. Besides, this study provides music therapy for 20 min. During the observations, some respondents displayed signs of boredom with children asking to stop the music therapy before completing the music therapy session. This can lead to the ineffectiveness of music therapy. The best approach in providing music therapy is to let the patient adjust the frequency, duration, and timing of the music intervention directly.⁴¹

Clinically, music therapy influenced the decrease in salivary cortisol levels. This is supported by several studies that explain that music therapy has a positive effect on salivary cortisol levels.^{25,28,32,37,42,43} The sound of music accepted and perceived by the brain will stimulate the hypothalamus, which will then stimulate the pituitary to produce endorphins. Endorphin is an endogenous morphine that acts as the body's natural analgesic and also serves to protect/relieve the body from stressful conditions.^{10,27}

This study conducted a pretest before the music therapy and posttest after the music therapy, a comparison of dependent variables from the same experimental group can be made and the treatment results can be understood more accurately. We suggest further research with better methods, a larger sample size, a homogeneous population, and stress level, a conducive environment during an intervention, and consideration of the time and a shorter duration of music therapy that is less than 20 min in children.

Conclusion

Although the results of this study were not statistically significant, this study proved that clinically, music therapy influenced in reducing salivary cortisol levels, hence this study still recommends the use of music therapy as a complementary therapy that can be administered to children with leukaemia prior to getting an IV-line insertion to prevent the stress response in children.

Source of funding

This research is supported and funded by the Ministry of Finance, Republic of Indonesia, through *Beasiswa Unggulan Dosen Indonesia Dalam Negeri* (BUDI-DN) LPDP.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This study received ethical approval from the Ethical Committee of Medicine and Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta on 15 December 2017, Number KE/FK/1295/EC/2017.

Authors contributions

IH, SM, and FH conceived the study. IH and ZH drafted the manuscript, and SM and FH critically revised the manuscript for important intellectual content. IH collected samples and analysed the data. SM and FH facilitated all project-related tasks. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

References

1. Ward E, Desantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA - Cancer J Clin* **2014**; 64(2): 83–103.
2. Naghavi M. The global burden of cancer 2013. *JAMA Oncol* **2015**; 1–23.
3. Ali K, Sutaryo, Purwanto I, Mulatsih S, Supriyadi E, Widjajanto H, et al. Yogyakarta pediatric cancer registry: an international collaborative project of University Gadjah Mada, University of Saskatchewan, and the Saskatchewan Cancer Agency. *Asian Pac J Cancer Prev* **2010**; 11: 131–136.
4. Supriyadi E, Widjajanto PH, Purwanto I, Cloos J, Veerman AJP, Sutaryo S. Incidence of childhood leukemia in Yogyakarta, Indonesia, 1998–2009. *Pediatr Blood Canc* **2011**; 57(4): 588–593.
5. Handian FI, Widjajanto PH, Sumarni D. Motivasi, Hambatan, dan Strategi Orangtua Keluarga Miskin Dalam Merawat Anak Dengan Leukemia Limfoblastik Akut (LLA). *J Care* **2017**; 5(1): 1–9.
6. Hildenbrand AK, Clawson KJ, Alderfer MA, Marsac ML. Coping with pediatric cancer: strategies employed by children and their parents to manage cancer-related stressors during treatment. *J Pediatr Oncol Nurs* **2011**; 28(6): 344–354.
7. Zingg W, Pittet D. Peripheral venous catheters: an under-evaluated problem. *Int J Antimicrob Agents* **2009**; 34: 38–42.
8. Bennett Humphrey G, Boon Chris MJ, Chiquit van Linden van den Heuvel GFE, van de Wiel Harry BM. The occurrence of high levels of acute behavioral distress in children and adolescents undergoing routine venipunctures. *Pediatrics* **1992**; 90: 87–91.
9. Twycross A, Parker R, Williams A, Gibson F. Cancer-related pain and pain management: sources, prevalence, and the experiences of children and parents. *J Pediatr Oncol Nurs* **2015**; 32(6): 369–384.
10. Sherwood L. In: Sherwood L, editor. *Fundamental of human physiology*. 4th ed. Belmont: Brooks/Cole; 2012.
11. Selye H. The nature of stress. In: Seaward BL, editor. *Managing stress; principles and strategies for health and well-being*. 9th ed. Jones & Bartlett Learning; 2017. pp. 2–26.
12. Nicolson NA. Measurement of cortisol. In: Leucken LJ, Gallo LC, editors. *Handbook of physiological research methods in health psychology*. 1st ed. SAGE Publication; 2008. pp. 37–73.
13. Ivković N, Božović , Račić M, Grubač DP, Davidović B. Biomarkers of stress in saliva. *Sci J Fac Med Niš* **2015**; 32(2): 91–99.

14. McCarthy AM, Hanrahan K, Scott LM, Zemblidge N, Kleiber C, Zimmerman MB. Salivary cortisol responsivity to an intravenous catheter insertion in children with attention-deficit/hyperactivity disorder. *J Pediatr Psychol* **2011**; 36(8): 902–910.
15. Lee DY, Kim E, Choi MH. Technical and clinical aspects of cortisol as A biochemical marker of chronic stress. *BMB Rep* **2015**; 48(4): 209–216.
16. Kirschbaum H. Salivary cortisol in pschycobiological research: an overview. *Neuropsychobiology* **1989**; 22: 150–169.
17. Hellhammer DH, Wu S, Kudielka BM. Salivary cortisol as a biomarker in stress research. *Psychoneuroendocrinology* **2009**; 34: 163–171.
18. Rashkova M, Kalchev P, Emilova R, Ribagin L, Stoeva I. Cortisol in saliva - a marker for increased anxiety in children. *J IMAB* **2010**; 16(14): 67–69.
19. Lupien SJ. *How to measure stress in human*. 2nd ed. Centre for Studies on Human Stress; 2013. pp. 1–28.
20. Stouffer JW, Shirk BJ, Polomano RC. Practice guidelines for music interventions with hospitalized pediatric patients. *J Pediatr Nurs* **2007**; 22(6): 448–456.
21. Pfaff VK, Smith KE, Gowan D. The effects of music-assisted relaxation on the distress of pediatric cancer patients undergoing bone marrow aspirations. *Child Health Care* **2010**; (April 2015): 37–41.
22. Nguyen TN, Nilsson S, Hellström A-L, Bengtson A. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. *J Pediatr Oncol Nurs* **2010**; 27: 146–155.
23. Klassen TP, Curtis S. Music to reduce pain and distress in the pediatric emergency department: a randomized clinical trial. *JAMA Pediatr* **2013**; 167(9): 826–835.
24. Calcaterra V, Ostuni S, Bonomelli I, Mencherini S, Brunero M, Zambaiti E, et al. Music benefits on postoperative distress and pain in pediatric day care surgery. *Pediatr Rep* **2014**; 6: 44–48.
25. Schwilling D, Vogeser M, Kirchhoff F, Schwaiblmair F, Boulesteix A, Schulze A, et al. Live music reduces stress levels in very low-birthweight infants. *Acta Paediatr* **2015**; 104: 360–367.
26. Kim J, Stegemann T. Music listening for children and adolescents in health care contexts: a systematic review. *Arts Psychother* **2016**; 51: 72–85.
27. Rokade PB. Release of endomorphin hormone and its effects on our body and moods: a review. In: *International Conference on Chemical, Biological and Environment Sciences (ICCEBS)*; 2011. pp. 436–438.
28. Koelsch S. Effects of music listening on cortisol levels and propofol consumption during spinal anesthesia. *Front Psychol* **2011**; 2(April): 1–9.
29. Robb SL, Carpenter JS, Burns DS. Reporting guidelines for music-based interventions. *J Health Psychol* **2010**; 16(2): 342–352.
30. Mrázová M, Celec P. Reviews A systematic review of randomized controlled trials using music therapy for children. *J Alternative Compl Med* **2010**; 16(10): 1089–1095.
31. *Instructions for use salivary cortisol ELISA*; 2016. Germany.
32. Leardi S, Pietroletti R, Angeloni G, Necozone S, Ranalletta G, Gusto B Del. Randomized clinical trial examining the effect of music therapy in stress response to day surgery. *Br J Surg* **2007**; 65(94): 943–947.
33. Cameron A, Henley D, Carrell R, Zhou A, Clarke A, Lightman S. Temperature-responsive release of cortisol from its binding Globulin: a protein thermocouple. *J Clin Endocrinol Metab* **2010**; 95(10): 4689–4695.
34. Juutilainen A, Hämäläinen S, Niemenpää J, Kuittinen T, Pulkki K, Koivula I, et al. Serum cortisol and inflammatory response in neutropenic fever. *Ann Hematol* **2011**; 90(12): 1467–1475.
35. Wrosch C, Miller GE, Schulz R. Cortisol secretion and functional disabilities in old age: importance of using adaptive control strategies. *Psychosom Med* **2009**; 71(9): 996–1003.
36. Good M, Albert JM, Arafah B, Anderson GC, Wotman S, Cong X, et al. Effects on postoperative salivary cortisol of relaxation/music and patient teaching about pain management. *Biol Res Nurs* **2012**; 15(3): 318–329.
37. Migneault B, Girard F, Albert C, Chouinard P, Boudreault D, Provencher D, et al. The effect of music on the neurohormonal stress response to surgery under general anesthesia. *Anesth Analg* **2004**; 98(2): 527–532.
38. Rodin G, Yuen D, Mischitelle A, Minden MD, Brandwein J, Schimmer A, et al. Traumatic stress in acute leukemia. *Psycho Oncol* **2011**; 22(2): 299–307.
39. Lopes-Junior LC, Bomfim EO, Nascimento LC, Nunes MDR, Pereira-Da-Silva G, Lima RAG. Non-pharmacological interventions to manage fatigue and psychological stress in children and adolescents with cancer: an integrative review. *Eur J Canc Care (Engl)* **2016**; 25(6): 921–935.
40. Zhang J, Wang P, Yao J, Zhao L. Music interventions for psychological and physical outcomes in cancer: a systematic review and meta-analysis. *Support Care Canc* **2012**; 20: 3043–3053.
41. Chlan LL, Weinert CR, Heiderscheid A, Tracy MF, Skaar DJ, Guttormson JL, et al. Effects of patient-directed music intervention. *J Am Med Assoc* **2013**; 309(22): 2335–2344.
42. Slopen N, McLaughlin KA, Shonkoff JP. Interventions to improve cortisol regulation in children: a systematic review. *Pediatrics* **2014**; 133: 312–326.
43. Khalfa S, Bella SD, Roy M, Peretz I, Lupien SJ. Effects of relaxing music on salivary cortisol level after psychological stress. *Ann N Y Acad Sci* **2003**; 999: 374–376.

How to cite this article: Hasanah I, Mulatsih S, Haryanti F, Haikal Z. Effect of music therapy on cortisol as a stress biomarker in children undergoing IV-line insertion. *J Taibah Univ Med Sc* 2020;15(3):238–243.