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Impact of IV-line Insertion on Salivary Cortisol Levels as a Stress Biomarker in Children

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Abstract

BACKGROUND: Children with leukemia will be treated for a quite long period of time that they will be subjected to multiple invasive procedures, one of which is IV-line insertion. This procedure can cause stress, which increases cortisol levels in the body.

AIM: This study aimed to investigate how IV-line insertion affected cortisol levels as a stress biomarker in children.

METHODS: This is a single-group pre-test and post-test design pre-experimental study. The study enrolled 30 children undergoing IV line insertion, aged from 6 to 18 years, who had not been eating or drinking for 30 min before the saliva sampling was scheduled to get IV-line insertion. The ELISA test was used to measure the salivary cortisol. If the difference in the cortisol levels is > 0.05 ng/ml, it is clinically significant. Furthermore, the Wilcoxon test was used to analyze the data. Cortisol changes were considered statistically significant if the p-value was <0.05.

RESULTS: The cortisol levels were 3.43 (0.19–16.67) ng/ml and 4.14 (0.19–16.67) ng/ml before and after IV-Line insertion, respectively. The difference in the median was 0.71 ng/ml. The > 0.05 ng/ml difference indicates that IV-line insertion affects cortisol elevation. The Wilcoxon test showed a value of p = 0.34 (p > 0.05) indicating that IV-line insertion had no statistically significant effect on cortisol.

CONCLUSION: Although an IV-line insertion does not have a statistically significant effect on cortisol, it clinically influences the increase of cortisol in children with leukemia.

Introduction

Cancer is the second leading cause of death after accidents among children aged 1–14 years. Of about 1190 children suffering from cancer, it is estimated that almost 50% of adolescents will die from cancer in 2021 [1]. The typical cancer that attacks children worldwide, including in Indonesia is leukemia [1], [2], [3]. From 2008 to 2017, the incidence of leukemia increased in children and adolescents by about 1% per year [1]. Children with leukemia will go through a long series of treatments and diagnostic procedures. Prolonged treatment, repeated hospitalizations, high treatment costs, cancer diagnosis, and many invasive procedures performed during the treatment process are stressful for children [4], [5].

Invasive procedures involving the insertion of needles, such as lumbar puncture, bone marrow aspirations, bone marrow puncture, IV-line insertion, and blood sample, will be used on children with leukemia during treatment [5]. One of the most common invasive procedures performed on children with leukemia is the insertion of an IV line. When in the hospital, 30–80% of patients are planned to have intravenous IV-line insertion procedures [6]. According to a clinical study, 51% of children and 83% of children under the age of five experience discomfort during regular vein insertion [7]. Twycross *et al*., (2015) did a systematic study and found that invasive procedures, rather than the symptoms of the disease, cause more pain in children with cancer [8].

The insertion of an IV-line can cause pain and can prompt a child's to show behavioral and physiological responses. The changes in behavioral responses include sobbing, vomiting, and verbal complaints. Meanwhile, increased blood pressure, stress hormones, muscle tension, and sweating are some forms of the physiological responses [9], [10]. Stress monitoring is critical to provide a comprehensive picture of the child's status, so health-care providers can intervene quickly and effectively. The measurement of the hormone cortisol is one of the objective indicators of stress levels. This method is particularly useful for children who are unable to express their emotions since it can identify invisible stress levels. The elevated cortisol level is an indicator of acute or chronic stress [9], [11], [12]. Salivary cortisol techniques have

the advantages of being simple to collect, non-invasive, quick, and repeatable [13]. In determining adrenocortical function, salivary cortisol is a better, more effective, and more reliable test than blood tests [13], [14].

When children undergo an IV-line insertion procedure, they will rather feel uncomfortable due to the treatment than due to the disease's symptoms. This may make children feel anxious of the needles, so they avoid medical treatments and procedures [15]. Furthermore, it can indirectly affect children's quality of life, as well as increasing morbidity and mortality [16]. Because repeated IV-line insertions in children with leukemia can worsen their health, salivary cortisol testing is required to evaluate their stress level. The results of the study can be used as an evidence that IV-line insertion can increase children's stress levels, therefore, it can be used as a reference for health-care providers for monitoring children's stress levels and taking appropriate steps to minimize it. This study aimed to investigate how IV-line insertion affects cortisol levels as a biological indicator of stress in children with leukemia.

Methods

Design

This is a single-group pre-and post-test design pre-experimental study. The study was carried out after it was accepted by Gadjah Mada University's Ethics Committee and the permission was granted by the authorities in charge of the research site's management.

Participant and sample size

Children with leukemia in the Dr. Sardjito General Hospital Yogyakarta's Pediatric 1 Day Care and Estella (pediatric cancer) wards from January to February 2018 were studied. Dr. Sardjito General Hospital Yogyakarta is a national referral hospital with an integrated oncology center. The main criteria for the sample of this study were children 6–18 years of age with leukemia who had an IV line insertion and had not been eating or drinking for 30 min before saliva sample was taken. All children who met the inclusion criteria were included in the study. The exclusion criteria within this study were children who were not at the research site and the children who did not want to be respondents. This study has a 0.05, 95% confidence interval, and an 80% research power. The previous studies using large numerical analytic sample formulations in pairs with repeated measurements of more than twice measurements led to the sample size determination. From the results of these calculations, the final respondents of this study were 30 respondents.

Instrument

ELISA kit 96 wells DES661 were used to measure salivary cortisol levels. The researcher collected saliva, while clinical pathology laboratory staff at UGM Yogyakarta measured salivary cortisol concentrations.

Procedure

When the researchers had taken the saliva samples, salivary cortisol levels were measured at the Faculty of Medicine Gadjah Mada University's Clinical Pathology department. The research was divided into three stages: Pre-intervention, intervention, and post-intervention.

Pre-intervention stage

Medical records were examined to learn about respondents' names, ages, genders, and drugs are taken, comorbidities (such as anemia, fever, sepsis, or other comorbidities), and IV-line insertion rates. We also did a screening for emergency conditions (loss of consciousness, shortness of breath, dizziness, or acute pain) and the last meal/drink consumed by the participants. Patients were not allowed to eat or drink for 30 min before saliva sampling and the duration of this study. Subsequently, the researchers explained the research's objectives, benefits, and methods, as well as the opportunity to participate as research subjects. After that, the patients or their families were asked to sign a consent form if they agreed to participate.

Intervention stage

At this stage, the participants received an IV-line insertion. The first saliva sample was collected 10–20 min before insertion of the IV line, meanwhile the second saliva sample was collected 10–20 min after insertion of the IV line.

Post-intervention stage

At this stage, the patients prayed, and they received positive reinforcement.

Data analysis

The effect of IV line insertion on salivary cortisol levels was examined by comparing the data before and after the IV line insertion and analyzing the difference in mean of salivary cortisol levels. To ensure that the cortisol level variation was due to IV Line insertion, we first analyzed the external variables which are probable to influence the salivary cortisol levels such as age, sex, comorbidities, drug usage, and needle insertion frequency.

The data of respondents' characteristics were analyzed using univariate analysis, and the results were presented in the form of a frequency table (n) and percentages. The Mann–Whitney test and the Kruskal–Wallis test were used to examine the effect of an external variable on salivary cortisol levels statistically. The Wilcoxon test was used to see how IV line insertion affected cortisol levels. The study employed $\alpha < 0.05$, 95% CI, 80% research power, and a $p < 0.05$ was considered significant. In clinical practice, a difference of 0.05 ng/ml is considered significant for an increase or decrease in cortisol levels [17].

Ethics

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

Results

Thirty-one patients met the inclusion requirements; however, one of them had an error on the cortisol test. Figure 1 shows the findings of monitoring each respondent's salivary cortisol levels before and after the IV-line was inserted.

According to the chart above, salivary cortisol levels in participants range from 0.2 to 16.6 ng/ml. Cortisol levels increased in the majority of respondents after IV-line insertion. The effect of external variables on salivary cortisol levels is shown in table.

Table 1 shows the results of the analysis of the effect of external variables on cortisol levels. Table 1 shows that all factors have $p > 0.05$, indicating that all variables have no effect on cortisol levels and that any variations in cortisol levels are due to IV-line insertion.

Table 1: 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)	Median (min-max)	
Age				
Children (23)	2.95 (0.19–16.67)	4.61 (0.25–9.89)	0.07 (7.08–8.43)	0,53[a]
Adolescent (7)	3.93 (0.25–6.65)	3.68 (0.35–7.28)	0.10 (3.35–2.87)	
Sex				
Male (20)	3.95 (0.19–16.67)	6.02 (0.26–9.89)	0.26 (7.08–8.43)	0.14[a]
Female (10)	2.91 (0.25–9.77)	2.19 (0.25–9.68)	−0.07 (3.35–5.16)	
Drugs consume				
Yes (26)	2.91 (0.19–16.67)	3.46 (0.25–9.68)	0.08 (7.08 –8.43)	1.00[a]
No (4)	6.61 (4.60–9.77)	6.21 (4.61–9.89)	0.30 (3.90 –5.16)	
Comorbidities				
Yes (21)	3.56 (0.19–16.67)	4.17 (0.25–9.89)	-0.06 (7.08 –8.43)	0.40[a]
No (9)	3.31 (0.52–5.80)	4.12 (0.61–8.02)	0.31 (−3.80–1.36)	
Frequency insertion				
1 (24)	3.81 (0.19–16.67)	4.97 (0.25–9.89)	0.07 (3.90–8.43)	0.27[b]
2 (4)	1.85 (0.52–6.56)	1.80 (0.61–3.68)	−0.18 (0.36–2.87)	
4 (2)	1.42 (0.25–2.60)	5.01 (0.35–9.68)	3.59 (7.08–0.10)	

Min: minimum; max: maximum; (*) P value<0.05 is significant; (a) analyzed by Mann–Whitney test, (b) analyzed by Kruskal–Wallis test.

Table 2 shows the findings of the analysis of the influence of IV-line insertion on cortisol levels.

Table 2: The effect of IV line insertion on salivary cortisol levels (n = 30)

Cortisol ng/ml	Mean differences	
	Median (Min-max)	p-value
Before IV-line insertion	3.43 (0.19–16.67)	
After IV-line insertion	4.14 (0.25–9.89)	0.34*

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

The median difference before and after IV-line insertion was 0.71 ng/ml, which was the result of a 3.43 ng/ml in cortisol levels before IV-line insertion and 4.14 ng/ml in cortisol levels after IV-line insertion (Table 2). This means that the difference between the two measures is >0.05 ng/ml, indicating that IV-line insertion had a clinical effect on salivary cortisol levels. The Wilcoxon analysis shows $p > 0.05$, indicating that there was no a statistically significant effect of IV-line insertion on cortisol levels.

Discussion

Our study revealed that The IV-line insertion caused variations in cortisol levels. The results of this

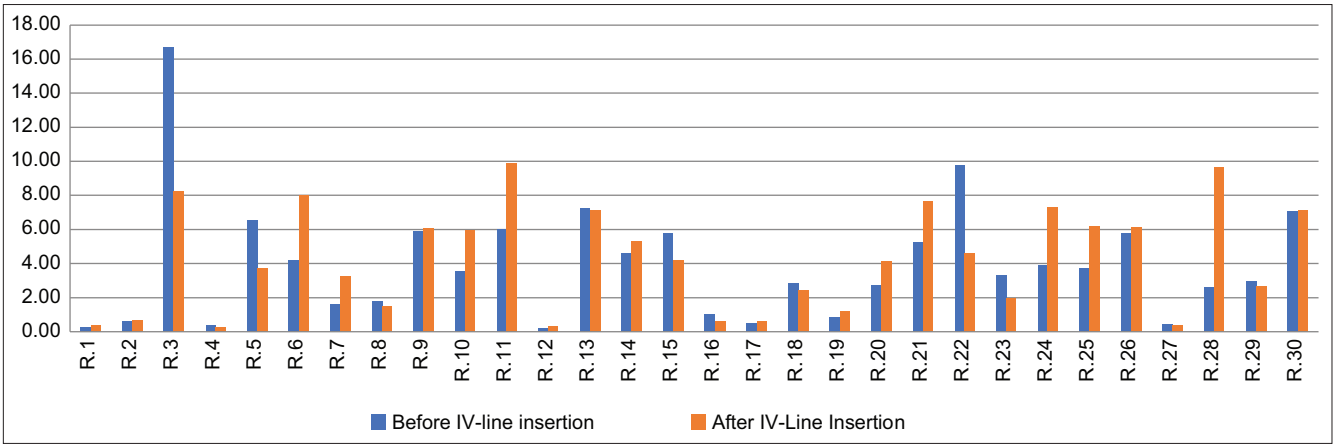

Figure 1: Salivary cortisol levels before and after IV-line insertion

study negate the finding of multiple previous studies which suggest that cortisol levels are affected by age, sex, comorbidities, and the frequency of needle insertion. Cortisol levels rise due to the age, men have a higher cortisol reaction than women following stress [18]. Acute and chronic comorbidities, endocrine, and immunological illnesses all have a major impact on cortisol levels [19]. Venous insertion frequency is also linked to higher cortisol levels [20]. The results of this study suggested that IV-line insertion had a clinical effect on salivary cortisol levels. In contrast, several previous studies have argued against the point. McCarthy *et al*. (2009) assessed children's physiological responses to stress as measured by an increase in salivary cortisol levels on arrival to the clinic and 20 min following intravenous insertion [21].

The findings of this study revealed that the salivary cortisol levels of the children with leukemia increased when measured 20 min after the intravenous insertion. The levels was higher than that when the patients came to the clinic. According to [22], cortisol release is the best hypothalamus-pituitary-adrenal axis marker in response to acute psychosocial stress. After the onset of stimulation, blood or salivary cortisol levels gradually rise within minutes (typically <10 min) and reach peak concentrations 10–30 min after the stress exposure is stopped [22]. When the body is exposed to physical, psychological, chemical, or social stress, the body's systems are affected physiologically. Almost all brain areas and receptors throughout the body will expose the hypothalamus to stress. The hypothalamus will immediately respond by releasing CRH, which will stimulate the release of ACTH and cortisol and vasopressin [10].

The findings in this study, as shown in Table 2, exposed that the insertion of an IV-line had no statistically significant effect on cortisol levels. This is most likely due to several reasons, including the small sample size and the presence of outliers like the cortisol level data, which is unique and significantly different from the data of other respondents. The range of salivary cortisol levels of respondents ranges from 0.2 to 16.6 ng/ml, as shown in Figure 1. The significant difference in cortisol levels between one respondent and the others could be due to several factors, including the homogeneity of stress exposure during the study, such as the frequency of needle insertion during IV-line insertion, the level of physical suffering, and the severity of disease among the study participants. The measurement of the cortisol levels of the participants was likely be affected by the homogeneity of stress exposure levels. Variations in the findings of salivary cortisol level measurement are impacted by factors affecting the child as well as familial factors. In addition, cortisol levels are influenced by a variety of characteristics in children, such as pain sensitivity, temperament, and experiences [19], [23]. Pain sensitivity differs from one child to the next. Children with low pain tolerance have high levels of cortisol. When a child is distressed or anxious, temperament/personality traits have a significant association with increased adrenocortical reactivity like cortisol [23].

Children with leukemia had lots of experiences with intravenous IV-line insertions during treatment, which might make them anxious. In school-aged children group, the previous IV-line insertion experience had a significant effect on pain levels [24]. The physiological reaction of children to stress is also strongly influenced by family support. Hugging the child, talking to him, asking the child to pray, teaching the child to take a deep breath, and distracting the child are all examples of family support given throughout the IV-line insertion process. Family support, namely, talking to children, laughing together, and telling stories, has been indicated to reduce pain in children [23]. McCarthy *et al*. studied the effects of parents utilizing distraction strategies on their children's stress levels. The study found that children who received parental distraction strategies were distressed [25].

McCarthy *et al*. did a literature analysis and mapped out several factors influencing children's stress responses such as higher cortisol levels at the time of IV-line insertion include (1) child variables, namely, age, gender, ethnicity, experience, temperament, coping methods, anxiety, sensitivity pain, and heredity; (2) parental characteristics such as gender, parenting style, experience, parental anxiety level, ethnicity, and distraction strategies taught to children by parents; and (3) anesthetics applied topically, such as EMLA or MLX4. Apart from these variables, McCarthy *et al*. had identified several other factors influencing stress responses during IV-line insertion, including the child's ethnicity, medical diagnosis, history of invasive procedures, and procedure preparation time [26].

The limitation of this study was that the researcher could not control the actions of parents in reducing pain and children's stress levels when the child underwent an IV line insertion, such as child's attention, parental touch, and other actions. In addition, the homogeneity of the level of stress exposure during the study was difficult for researchers to control, for example, the frequency of needle injection during IV line insertion, the level of physical suffering, and the severity of the disease variations among the participants. It can affect cortisol levels in children with leukemia. We suggest more studies to be conducted in this scope using better methods, larger sample sizes, homogeneous populations, and minimum confounding biased factors.

Conclusion

Although the results of this study were not statistically significant, it had shown that IV-line

insertion caused an increase in salivary cortisol levels in children with leukemia. Consequently, this study is still recommended as an objective evidence that IV-line insertion can cause stressful conditions in children undergoing insertion. Hence, the health workers can provide preventive intervention or strategy management to reduce stress the provide invasive medical procedures, particularly IV line insertion, to the children.

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