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Research

Differences Levels of Sodium, Potassium, Calcium, and Magnesium Before and After Cisplatin Administration in Child with Osteosarcoma

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ABSTRACT

Background: Cisplatin is one of the most commonly used cytostatic chemotherapy agents, especially in patients with solid tumors such as osteosarcoma. The exact mechanism of whether and how cisplatin causes electrolyte disturbances is still unclear. This study aims to determine the differences in levels of sodium, potassium, calcium, and magnesium with the administration of cisplatin in children with osteosarcoma.
Subjects and Method: This was an analytical retrospective study using secondary data in the form of medical records. The sample size in this study was calculated by the single proportion formula. The population was children with osteosarcoma who had been given cisplatin chemotherapy at Dr. Moewardi Hospital, Surakarta in January to March 2021. Total of 25 samples were included in this study. The variables studied included the administration of Cisplatin (independent variable) and electrolyte levels including sodium, magnesium, potassium and calcium (dependent variable). The research instrument used is medical records Data were analyzed using repated Anova test, Wilcoxon rank test, and post hoc test.
Results: There were differences and decreases in electrolyte levels before and after cisplatin administration in osteosarcoma patients, respectively: sodium ($p < 0.001$), potassium ($p = 0.002$), calcium ($p < 0.001$), and magnesium ($p < 0.001$). The greatest decrease in electrolyte levels occurred in the fourth cycle after administration of cisplatin, respectively: sodium (mean= -4.44; $p < 0.001$), potassium (Mean= -0.46; $p = 0.002$), calcium (Mean= -0.11, $p < 0.001$), and magnesium (Mean= -0.07, $p < 0.001$).
Conclusion: Cisplatin can interfere with electrolyte reabsorption in the renal tubules. Hypomagnesemia, hypokalemia, hypocalcemia and hyponatremia were found in children with osteosarcoma who received cisplatin. The decrease in electrolyte levels was greatest especially after undergoing the 4th cycle of chemotherapy. This was associated with repeated exposure in which the kidneys accumulated higher levels of cisplatin.

Keywords: osteosarcoma, cisplatin, electrolyte.

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BACKGROUND

Osteosarcoma is a primary malignancy caused by a tumor in the bone that is often experienced by children and adolescents (Arndt et al., 2012). In general, osteosarcoma is found in children aged 11-15

years where this tumor most often affects the metaphysis of long bones, especially the femur, proximal tibia, proximal fibula, proximal humerus, and pelvis. (Marcdante and Kliegman, 2014; Liamis et al., 2016; Windiastuti et al., 2018). According to the World Health Organization (WHO), osteosarcoma has an incidence rate of 45/ 1,000,000 cases per year. Based on basic research on Indonesian health in 2013, the prevalence of cancer was 1.4/mile % (Marcdante and Kliegman, 2014; Oronsky et al., 2017). In general, malignancy in children can be cured, but the approach to the management of malignancy in children is very complex. One of the treatments for malignancy in children is chemotherapy (Durfee et al., 2016; Misaghi et al., 2018) Although it has good effectiveness against cancer cells, Chemotherapy also has side effects, one of which is electrolyte disturbances (Liamis et al., 2016; Oronsky et al., 2017)

Platinum chemotherapeutic agents and their derivatives are one of the most frequent used cytostatic drugs, especially in patients with solid tumors such as osteosarcoma. One of the effects of this chemotherapeutic agent is electrolyte disturbances (Latcha, 2015; Shirali et al., 2016; Sihombing et al., 2016; Bowman, 2017), especially cisplatin which cause hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia (Oronsky et al., 2017; Oun et al., 2017; Shimada et al., 2018; Liu et al., 2019). In the majority of cases, electrolyte disturbances in children with malignancy are associated with clinical manifestations that can worsen the patient's condition to life-threatening state. The exact mechanism of whether and how cisplatin causes electrolyte disturbances, such as sodium, potassium, calcium, and magnesium is still unclear, but there is one study conducted by Ariceta et al that showed that cisplatin can induce hypomagnesaemia (Rosner and Dalkin, 2014; Oronsky *et al.*, 2017)

Existing research has focused only on magnesium disturbances caused by cisplatin but has limited data for other electrolyte disturbances associated with cisplatin regimens (Rosner and Dalkin, 2014; Oronsky et al., 2017; Berardi et al., 2019) There has not been any studies explaining relationship between other electrolyte disturbances, including studies in Indonesia (Rosner and Dalkin, 2014; Oronsky et al., 2017; Berardi et al., 2019). This study aims to determine differences in levels of sodium, potassium, calcium, and magnesium with cisplatin administration in children with osteosarcoma.

SUBJECTS AND METHOD

1. Study Design

This study is an analytical retrospective study using secondary data in the form of medical records of children with osteosarcoma who had been given cisplatin chemotherapy at Dr. Moewardi Hospital, Surakarta in January to March 2021.

2. Population and Samples

The population were pediatric patients who was diagnosed osteosarcoma and had been given cisplatin chemotherapy at Dr. Moewardi Hospital Surakarta. Total of 25 samples were included in this study. Sampling technique used is probability sampling by means of simple random sampling.

3. Study Variable

The variables studied in this study were the administration of Cisplatin with a dichotomous nominal scale as independent variable and electrolyte levels (contents of sodium, magnesium, potassium and calcium) with a numerical scale as dependent variable. The confounding variables that could be controlled in this study were concomitant drugs in addition to saline infusion and other comorbidities that could be excluded from observation, and which could not be controlled: saline infusion as a concomitant drug.

4. Operational Definition of Variables

Electrolyte levels, include sodium, potassium, calcium, and magnesium levels. Obtained from clinical laboratory measurements RSUD Dr. Moewardi Surakarta with a blood sample that includes levels.

Administration of cisplatin, measured using the dose of cisplatin obtained from the patient's medical record.

Drugs used concurrently in samples that can affect electrolytes, consisting of: diuretics, NSAIDs, opioids, insulin, saline infusion, MgSO4, Kcl, Ca Gluconas.

Comorbidities, accompanying diseases other than osteosarcoma, was obtained from the results of history taking, physical examination, and others.

5. Study Instrument

The medicine administration and medical condition of the patients were acquired from the medical record.

6. Data Analysis

Data were analyzed using Software Package for Social Science (SPSS) version 25 software. Bivariate analysis was analyzed using Friedman test, repeated Anova test, Wilcoxon rank test, pair t test with a significance level of 5%.

7. Research Ethics

This study was approved by the Health Research Ethics Committee of Dr. Moewardi Hospital, Surakarta, No 15/I/HREC/2021.

RESULTS

This study involved 25 pediatric patients with a diagnosis of osteosarcoma who had been given cisplatin chemotherapy at Dr. Moewardi Hospital Surakarta with the aim of whether there is a difference between the levels of sodium, potassium, calcium, and magnesium before and after administration of cisplatin in children with osteosarcoma. The instrument of this study was the medical records of osteosarcoma patients who had undergone cisplatin chemotherapy at Dr. Hospital. Moewardi Surakarta period January 2016 to January 2021. The characteristics of the research sample are showed in table 1 and a description of the electrolyte for each observation in table 2.

Table 1. Characteristics of Research Sample

Characteristics	Category		Frequency	Percentage
Sex	Male		17	68%
	Female		8	32%
Location of tumor	Lower extremity		15	60%
	Upper extremity		7	28%
	Others		3	12%
Tumor size	< 10 cm		16	64%
	> 10 cm		9	36%
	Mean	**SD**	**Min.**	**Max.**
Age (years)	7.52	1.69	4	10

This study was followed by the majority of male samples (68%) with the most tumor locations being in the lower extremity (60%) and with tumor size <10cm (64%). Meanwhile, in this study the sample has an age range of 4 to 10 years with mean of 7.52 and standard deviation of 1.69 years. The difference in levels of sodium, potassium,

and calcium before and after administration of cisplatin in children with osteosarcoma in this study using the Friedman test followed by the Wilcoxon rank test because there are results of the examination whose data when tested with the Shapiro Wilk test got a p value <0.05 or does not meet the normality assumption. Meanwhile, the difference in magnesium levels before and after administration of cisplatin in children with osteosarcoma in this study used the repated Anova test followed by the pair t test because there were examination results whose data when tested with the Shapiro Wilk test all obtained p>0.05 or met the normality assumption. Follow-up tests were carried out to find out the difference between rate sodium between before (pretest) and after administration of cisplatin (cycle 1, cycle 2, cycle 3, and cycle 4) partially. The results of examination of electrolyte levels before and after cisplatin administration in children with osteosarcoma can be seen in tables 2 and 3 as follows:

Table 2. Description (Univariate) and Simultaneous Difference Test of Electrolyte Level Examination Results Before and After Administration of Cisplatin

	Na(n=25)		K (n=25)		Ca (n=25)		Mg (n=25)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Pretest	133.28	2.72	3.31	0.27	1.08	0.09	0.38	0.05
Cycle 1	130.40	3.27	3.07	0.35	1.03	0.11	0.36	0.06
Cycle 2	132.28	4.38	3.00	0.57	1.05	0.09	0.35	0.05
Cycle 3	131.64	4.38	2.98	0.59	1.02	0.08	0.34	0.05
Cycle 4	128.84	5.13	2.85	0.62	0.97	0.14	0.30	0.06
p	<0.001*		0.002*		<0.001*		<0.001**	

* Friedman test, ** Repeated Anova test; significant at p<0.05

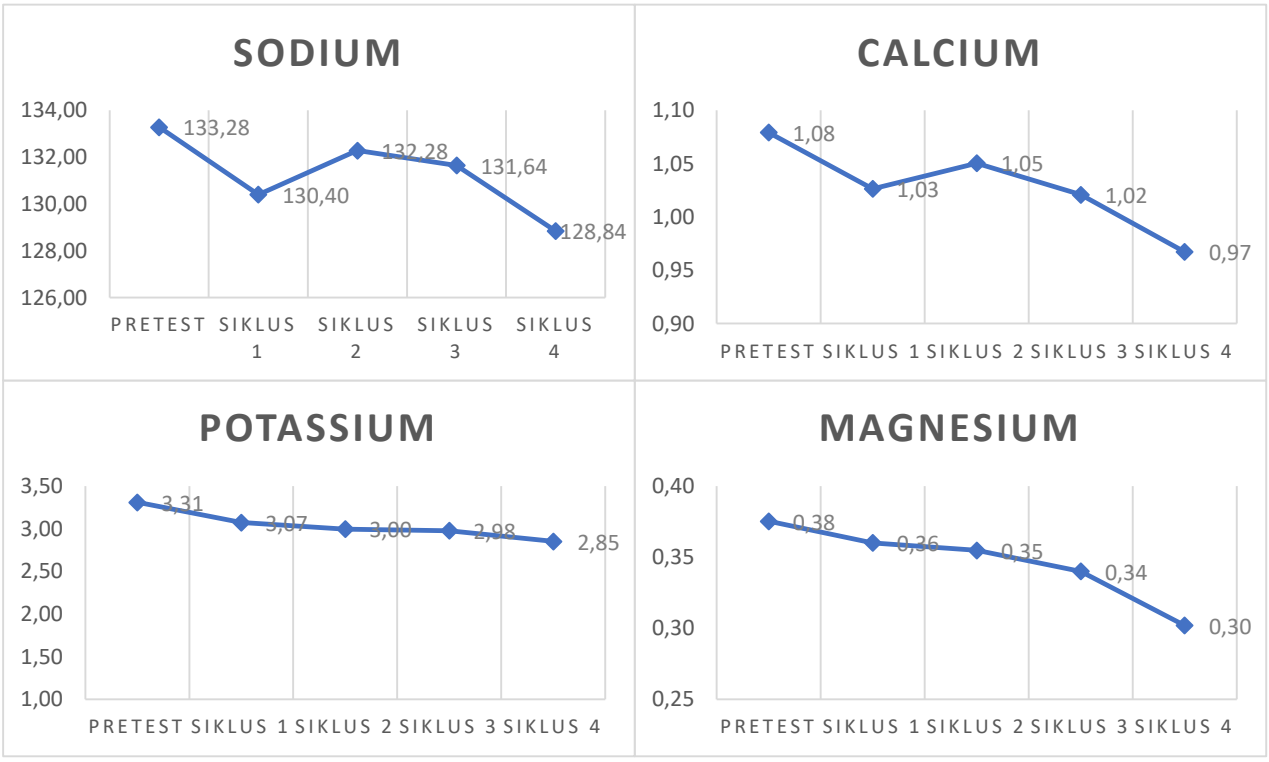

Figure 1. Estimated Marginal Means of Electrolyte Levels

Table 3. Partial difference test of electrolyte level examination results before and after administration of cisplatin

	Na(n=25)		K (n=25)		Ca (n=25)		Mg (n=25)	
	Mean	**p**	**Mean**	**P**	**Mean**	**p**	**Mean**	**p**
Pretest VS Cycle 1	-2.88	<0.001	-0.24	0.001	-0.05	<0.001	-0.02	0.028
Pretest VS Cycle 2	-1.00	0.082	-0.31	0.006	-0.03	0.021	-0.03	0.022
Pretest VS Cycle 3	-1.64	0.045	-0.33	0.011	-0.06	0.005	-0.04	0.017
Pretest VS Cycle 4	-4.44	<0.001	-0.46	0.002	-0.11	<0.001	-0.07	<0.001
Cycle 1 VS Cycle 2	2.78	0.006	-0.40	0.688	0.92	0.359	-0.01	0.608
Cycle 1 VS Cycle 3	1.50	0.134	-0.84	0.400	-0.46	0.647	-0.02	0.108
Cycle 1 VS Cycle 4	-1.60	0.109	-1.86	0.062	-2.42	0.015	-0.06	<0.001
Cycle 2 VS Cycle 3	-1.00	0.318	-0.23	0.819	-3.51	<0.001	-0.01	0.292
Cycle 2 VS Cycle 4	-3.25	0.001	-1.09	0.278	-3.10	0.002	-0.05	<0.001
Cycle 3 VS Cycle 4	-3.63	<0.001	-1.23	0.218	-2.13	0.033	-0.04	<0.001

*Wilcoxon rank test; **Test pair t test, significant at p<0.05

a) Differences in Sodium Levels

The mean sodium level before cisplatin treatment (pretest) was 133.28; SD= 2.72, while after administration of cispatlin in cycle 1, sodium levels decreased with mean= 130.40; SD= 3.27, cycle 2 sodium level slightly increase with mean= 132.28; SD= 4.38, cycle 3 sodium level decreased with mean= 131.64; SD= 4.38, and cycle 4 sodium level is the lowest with the mean= 128.84; SD= 5.13. The results of the simultaneously statistical test with the Friedman test showed a value of p <0.001, which means that there is a significant difference in changes in levels sodium before and after administration of cisplatin in children with osteosarcoma.

Figure 1 shows a decreasing trend of sodium, especially in the pretest vs. cycle 4. Based on table 3 it is known that the sodium content experienced a statistically mean decrease in Pretest vs Cycle 1 (mean= -2.88; p <0.001), Pretest vs Cycle 3 (mean= -1.64; p= 0.045), Pretest vs Cycle 4 (mean= -4.44; p= 0.045), Cycle 2 vs Cycle 4 (mean= -3.25; p= 0.001), and Cycle 3 vs Cycle 4 (mean= -3.63; p <0.001). Meanwhile, there was a statistically significant increase only in cycle 1 vs cycle 2 (mean= 2.78; p= 0.006). It is concluded that there is a decrease in the level of sodium after administration of cisplatin in children with osteosarcoma.

b) Differences in Potassium Levels

The mean potassium level before treatment with cisplatin (pretest) was 3.31; SD= 0.27, while after administration of cispatlin in cycle 1, Potassium levels decreased on the mean= 3.07; SD= 0.35, cycle 2 Potassium levels decreased on the mean= 3.00; SD= 0.57, cycle 3 Potassium level decreased again on the mean= 2.98 +0.59, and cycle 4 Potassium level is the lowest with the mean= 2.85; SD= 0.62. The results of simultaneously statistical tests with the Friedman test showed a value of p= 0.002, which means that there is a significant difference in changes in levels Potassium before and after administration of cisplatin in children with osteosarcoma.

Figure 1 shows a decreasing trend of potassium, especially in the pretest vs. cycle 4. Based on table 3 it is known that the potassium content experienced a statistically mean decrease in Pretest vs Cycle 1 (mean= -0.24; p= 0.001), Pretest vs Cycle 2 (mean= -0.31; p= 0.006), Pretest vs Cycle 3 (mean= -0.33; p=0.011), and Pretest vs Cycle 4 (mean= -0.46; p= 0.002). Meanwhile, other comparisons showed a decrease although

not statistically significant and there was no increase in all comparisons. This concludes that there is a decrease in the level of potassium after administration of cisplatin in children with osteosarcoma.

c) Differences in Calcium Levels

The mean calcium level before cisplatin treatment (pretest) was 1.08; SD= 0.09, while after administration of cispatlin in cycle 1, Calcium levels have decreased on the mean= 1.03; SD= 0.11, cycle 2 Calcium levels have slightly increased on the mean= 1.05; SD= 0.09, cycle 3 Calcium level decreased on the mean= 1.02; SD= 0.08, and cycle 4 Calcium level is the lowest with the mean= 0.97; SD= 0.14. The results of the simultaneously statistical test with the Friedman test showed a value of p = <0.001 (p<0.05), which means that there is a significant difference in changes in levels C alcium before and after administration of cisplatin in children with osteosarcoma.

Figure 1 shows a decreasing trend of calcium, especially in the pretest vs. cycle 4. Based on table 3 it is known that the calcium content experienced a statistically mean decrease in Pretest vs Cycle 1 (mean= -0.05; p <0.001), Pretest vs Cycle 2 (mean= -0.03; p= 0.021), Pretest vs. Cycle 3 (mean= -0.06; p= 0.005), Pretest vs. Cycle 4 (mean= -0.11; p <0.001), Cycle 1 vs. Cycle 4 (mean= -2.42; p= 0.015), Cycle 2 vs. Cycle 3 (mean= -3.51; p <0.001), Cycle 2 vs. Cycle 4 (mean= -3.10; p= 0.002), and Cycle 3 vs. Cycle 4 (mean= -2.13; p= 0.033). Meanwhile, other comparisons show a decrease even though it is not statistically significant and the increase is only found in cycle 1 vs cycle 2 which is not statistically significant either. This concludes that there is a decrease in the level of calcium after administration of cisplatin in children with osteosarcoma.

d) Differences in Magnesium Levels

The mean magnesium level before cisplatin treatment (pretest) was 0.38; SD= 0.05, while after administration of cispatlin in cycle 1, Magnesium levels have decreased on the mean= 0.36; SD= 0.06, cycle 2 Magnesium levels have decreased on the mean= 0.35; SD= 0.05, cycle 3 Magnesium levels decreased again on the mean= 0.3; SD= 0.05, and cycle 4 Magnesium levels is the lowest with the mean= 0.30; SD= 0.06. Simultaneous statistical test results with test repated Anova p <0.001, which means there is a significant difference in changes in levels of Magnesium before and after cisplatin administration in children with osteosarcoma.

Figure 1 shows a decreasing trend of magnesium, especially in the pretest vs. cycle 4. Based on table 3 it is known that the magnesium content experienced a statistically mean decrease in Pretest vs Cycle 1 (mean= -0.02; p= 0.028), Pretest vs Cycle 2 (mean= -0.03; p= 0.022), Pretest vs. Cycle 3 (mean= -0.04; p= 0.017), Pretest vs. Cycle 4 (mean= -0.07; p <0.001), Cycle 1 vs. Cycle 4 (mean= -0.06; p <0.001), Cycle 2 cs Cycle 4 (mean= -0.05; p <0.001), and Cycle 3 vs Cycle 4 (mean= -0.04; p <0.001). Meanwhile, other comparisons showed a decrease, although not statistically significant and there was no increase in all comparisons. It is concluded that there is a decrease in the level of magnesium after administration of cisplatin in children with osteosarcoma.

DISCUSSION

This study was conducted to detect differences in electrolyte levels, including sodium, potassium, calcium, and magnesium before and after administration of cisplatin in children with osteosarcoma. Cisplatin itself is a chemotherapy drug that has long been used as a treatment for solid tumors, one of which is osteosarcoma. Cisplatin may accumulate in the kidneys. Nephrotoxicity associated with cisplatin administration has been reported for many years. The exact mechanism is not yet fully

understood. However, it is believed to be associated with the incidence of AKI involving the proximal tubule, oxidative stress, inflammation, renal vascular injury, acute tubular necrosis, and apoptosis in the proximal tubule.

One third of patients treated with cisplatin develop renal impairment within a few days of the initial dose. Renal susceptibility to cisplatin toxicity is thought to be due to its function as a major excretory organ for platinum. Due to its low molecular weight and uncharged state, cisplatin is freely filtered through the glomerulus and is secreted by tubular epithelial cells, and accumulates in the proximal and distal tubules where it exerts its nephrotoxic effects, particularly on the S3 segment of the proximal tubule.

From the results of this study, there were differences in the levels of sodium, potassium, calcium, and magnesium before and after cisplatin administration. Table 2 shows that there is a significant difference in changes in sodium levels before and after cisplatin administration in children with osteosarcoma where in the 4th cycle there was the most decrease, namely -4.44 and statistically significant with $p < 0.001$.

Pre-existing theories suggest that hyponatremia, although rare in cisplatin-treated patients, is associated with SIADH and Renal Salt Wasting are two possible mechanisms of cisplatin-induced hyponatremia. From the observation in cycle 2, it was found that there was an increase in sodium levels but not statistically significant with p value = 0.082, this was associated with the possibility of normal saline infusion given before cisplatin chemotherapy.

According to the results of the next electrolyte study regarding potassium, there were differences in potassium levels before and after cisplatin administration in children with osteosarcoma which were statistically significant with p= 0.002. Based on table 3 it can be concluded that the greatest decrease in potassium levels occurred in cycle 4. This is in line with previous findings, namely in the Journal of Research in Medical Science in 2015 which revealed that the most common electrolyte disturbances found due to cisplatin administration were hypokalemia as well as hypomagnesaemia (Anand, 2015).

The increase in renal absorptive capacity in response to decreased intestinal calcium absorption is the explanation behind cisplatin-induced hypokalemia. Hypomagnesemia can also cause Mg++-dependent Na, K-ATPase damage due to high sodium loss in cells, which, when combined with decreased renal potassium stores, leads to hypokalemia. In a study conducted by Rodriguez et al. (1989) it was stated that refracttory hypokalemia was closely related to uncorrected hypomagnesaemia (Rodriguez, 1989).

Hypocalcemia is also a side effect that is not uncommon with cisplatin chemotherapy. In the population of this study, which is depicted in table 3, it was found that the average decrease in calcium levels was obtained, with the largest decrease in cycle 4 and statistically significant with $p < 0.010$. The possible mechanisms behind this decrease in calcium levels are excessive loss of calcium in the urine, decreased renal tubular reabsorption of calcium due to tubular damage, due to low tissue response to parathormone, and low serum magnesium levels, this is in accordance with the theory proposed by Barton. et all in 2017 (Barton et al., 2018).

Hypomagnesemia is the most common side effect of cisplatin chemotherapy. In this study, it was found that there was a significant difference in changes in magnesium levels before and after cisplatin administration in children with osteosarcoma. On

average, the greatest decrease in magnesium levels occurred in cycle 4. Based on table 2 with a p <0.001 in other words, there was a significant difference in changes in magnesium levels before and after cisplatin administration in children with osteosarcoma. Direct injury to renal magnesium reabsorption in the ascending loop of Henle and distal tubule, is a possible mechanism behind cisplatin-induced hypomagnesemia.Cisplatin causes damage to magnesium receptors in the ascending branch of the loop of Henle and the distal tubule, causing tubular cell necrosis that impairs the magnesium reabsorption mechanism.

From this study we found that cisplatin can interfere with electrolyte reabsorption in the renal tubules. hypomagnesemia, hypokalemia, hypocalcemia and hyponatremia were found in children with osteosarcoma who received cisplatin. The decrease in electrolyte levels was greatest especially after undergoing the 4th cycle of chemotherapy. This was associated with repeated exposure in which the kidneys accumulated higher levels of cisplatin. The limitation of this study is that confounding factors cannot be controlled, such as the administration of infusion in the form of D5 NS and D5 NS during hydration before chemotherapy and after chemotherapy, so that it can affect the results of sodium electrolyte levels which are included in the research subject.

AUTHOR CONTRIBUTION

Hendra Wardhana was the main author who conducted the study, processed data analysis, and wrote the manuscript. Muhammad Riza examined the background and discussion of the study dan Husnia Auliyatul Umma formulated the framework of study.

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This study is self-funded.

CONFLICT OF INTERESTS

There is no conflict of interest in this study.

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