Original Article

Effect Of Selenium On Stress Oxidative In ASD Children

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Abstract

Background: Oxidative stress in autism spectrum disorder (ASD) children causes developmental disorders in ASD children. Administration of selenium to a mouse model of ASD can reduce oxidative stress. Studies on the effects of selenium on oxidative stress in ASD children is still limited. This study aims to evaluate the effect of selenium administration on oxidative stress in ASD children

Methods and Results: Randomized controlled trial study conducted in children with ASD. The study divided the participants into 3 groups with random allocation, namely the selenium I intervention group (n=22), the selenium 2 intervention group (n=22) and the control group (n=21). Selenium is given in the form of supplements and functional foods for 12 weeks. Oxidative stress was assessed by examining glutathione peroxidase (GPx) levels. Wilcoxon test, Kruskal-Wallis test, and Man-Whitney U test used in this study.

Results: The mean changes in GPX levels after intervention in the intervention group 1, intervention group 2, and the control group were 5.08, 5.79, and 9.73, respectively. There was no significantly difference in changes in GPX levels after administration of selenium.

Conclusion: Selenium could not decrease oxidative stress significantly in ASD children.

Keywords: autism spectrum disorder, glutathione peroxidase, oxidative stress, selenium

Introduction

The incidence of autism spectrum disorder (ASD) which is a group of neurodevelopmental disorders, is found to increase every year [1] . Autism prevalence that ranges within and across regions, with a median prevalence of 100/10,000 [2]. Africa and Australia have the ASD prevalence around the word [1]. The incidence of ASD in children can be detected at the age of less than two years [3–5]. Children with autism spectrum will cause symptoms of disturbances in their development, especially in the development of social interaction, communication and behavior [3–5].

The presence of oxidative stress is thought to be involved in the pathophysiology of signs and symptoms in children with ASD [6–8]. Increased oxidative stress has been observed in the brains of children with ASD [9].Oxidative stress is defined as an imbalance between the production of oxidant and antioxidants [10]. ASD children are more vulnerable to oxidative stress because of their imbalance in intracellular and extracellular glutathione levels and decreased glutathione antioxidant reserve capacity [7].

A recent systematic review study found that selenium can increase glutathione capacity level in adult [10]. However, studies indicate an imbalance in trace element homeostasis is important risk factor for ASD [3, 11]. Recent studies have shown that ASD children have significantly lower selenium (Se) levels in their hair and blood than children without ASD [12–15]. Selenium and selenium-dependent proteins are essential in brain development and managing oxidative damage in the brain, and it has been suggested that dyshomeostasis in selenium may be associated with ASD incidence [16].

Study on ASD mice model found that there was a decrease in oxidative stress after being given selenium [17]. Study on selenium administration to reduce oxidative stress in ASD children is still limited, therefore this study will evaluate the effect of selenium on oxidative stress in ASD children

Materials And Methods

This study used a randomized control trial (RCT) design. A total of 65 from 66 participants were involved in the study until the

end. They were randomly allocated into three groups (intervention 1 group (n=22), intervention 2 group (n=22), and the control group (n=21)) using block randomization, The sample size was estimated based on the study of Adams et al [18]. It was estimated that minimal of 22 participants in each group would provide 80% power to detect a 20score difference in the scale, with ά 0.05, allow a 10% drop out rate. A total of 65 participants were involved in the study and randomly allocated at the beginning of the study Participants were recruited from 14 different autistic clinics in East Java. All participants were ASD diagnosed by pediatricians at the clinic. Inclusion criteria were 2-6 years old. Exclusion criteria were children had Bel Palsy, heart disorders, and mental disorders.

The stress oxidative was analysed with the examination of GPx serum level in the laboratory before and three months

after the intervention. Analysis of IGPx using enzyme-linked immunosorbent assay (ELISA) method. GPx serum levels were expressed as micromol per litre (μmol/L).

Group intervention has given selenium., the group intervention 1 is given selenium supplement in powder form with a dose of 1 x 20 g/day, while group intervention 2 was given selenium in the form of food functional selenium-containing from heart cow with a dose of 50 grams/day. The control group was not given selenium, but they was given the modified cassava flour which was roasted for 15 minutes at a dose of 1 x 30 g/day. The packaging of selenium supplements and mocaf flour is carried out by pharmacists at pharmacies who have been accredited with Good Pharmacy Practice (GPP) in the same powder and packaging. Before and after the intervention the development of ASD children will be measured. The intervention was carried out for three months.

Data analysis using SPPS SBM version 25. Kolmogorov Smirnov test was used for determining normality distribution from continuous variables. Data displayed in the mean ± standard deviation. Comparison in the group before and after intervention using Wilcoxon test and the change after the intervention comparison between groups using a Kruskal-Wallis test and Mann Whitney U test.

The protocol was approved by the medical faculty, Diponegoro University ethics committee (ethical approval number No.238/EC/KEPK/FK-UNDIP/X/2020) and was performed following the principles expressed in the Declaration of Helsinki. This protocol was registered with clinical trial.gov (NCT 05218577). All participants gave written informed consent before participated in the study.

Results

About 65 ASD children participated in this study until the end of the study. All groups had homogeneous age (p=0.72), sex (0.895) and time of ASD diagnosis (p=0.865) at baseline (Table 1).

Table 1. Baseline characteristic of participants

Characteristics	Intervention 1 group	Intervention 2 group	Control group	P
Age (years)	3.95 ± 1.43	3.91 ± 0.97	3.71 ± 1.34	0.729*
Sex				
Male	19 (33.30)	19 (33.30)	19 (33.30)	0.895**
Female	3 (37.50)	3 (37.50)	2 (25,00)	
Age for first ASD diagnosis (years)	2.09 ± 0.47	2.04 ± 0.54	2.03 ± 0.47	0.865*

* Kruskal Wallis test, **Chi-Square test.

Figure 1 shows the GPx before and after intervention in all groups. Base on Wilcoxon test, there were no significantly GPx serum level before and after intervention in each group.

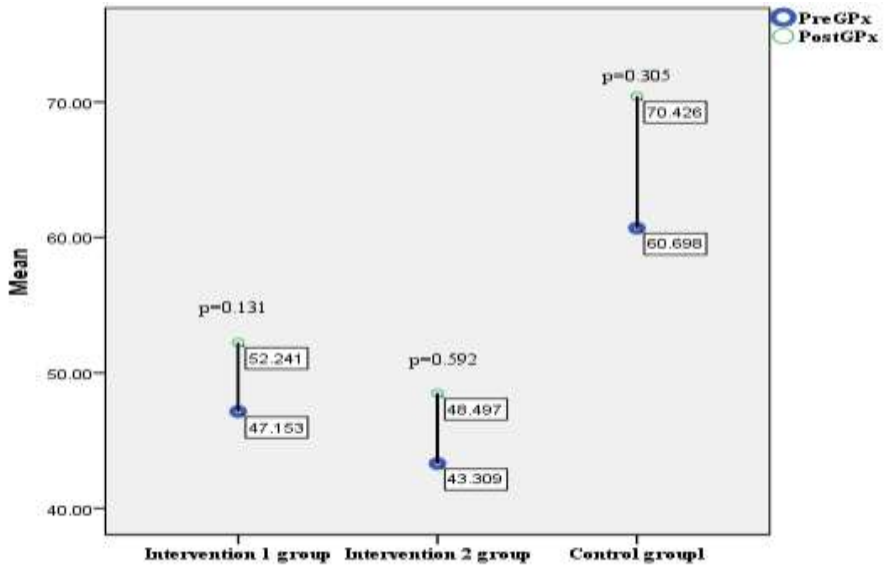

Figure. 1 Wilcoxon analysis of GPx serum level before and after intervention

Table 2. Kruskall-Wallis and Mann-Whitney post hoc analysis of Gpx serum level changing difference between the groups

Delta GPx	*Mean ± SD*	*P**
Intervention 1 group	5.09 ± 3.39	0.770
Intervention 2 group	5.19 ± 4.05	
Control group	9.73 ± 5.02	

*Kruskal-Wallis test. Mann-Whitney U test post hoc: Intervention 1 vs control (p=0.827),

Intervention 2 vs control (p=0.716)

Table 2 shows the GPx serum level changing after three months intervention. The mean changes in GPX levels after intervention in the intervention group 1, intervention group 2, and the control group were 5.08, 5.79, and 9.73, respectively. There was no significantly difference in changes in GPX levels after administration of selenium.

Discussion

The study aimed to evaluate the effect of selenium administration on the oxidative stress status of ASD children using GPx serum level as biomarker. The study found an increase in serum levels of GPx serum in the group given selenium, but this increase was not significant. However, the increasing of GPx serum level in both intervention group was not significantly difference with control group.

GPx is an enzyme antioxidant that very important to control the oxidative stress [9]. The increase of GPx level will help to decrease the oxidative stress in the brain of ASD children that can improve the severity of ASD [10]. Many recent studies have found a link between ASD and elevated oxidative stress, which may play a role in its development [6, 7].

As mentioned in the previous study, selenium contents in the hair and blood of children with ASD are significantly lower than non ASD children that associated with stress oxidative I ASD [12–15]. This study indicated that Se might be associated with the pathogenesis of ASD. As mentioned in the previous study, the improvement ASD mice following Se supplementation associated with the fact that Se supplementation altered monoamine neurotransmitter levels in brain tissue, reduced oxidative stress and neuroinflammation in hippocampal tissue, and relieved neural cell damage [17]. In the body, Se mainly exists in the form of selenoproteins [19]. The decrease level of selenoproteins causes irreversible oxidative stress injury in neurons [20]. The study in mice model, found that Se supplementation increased the expression of selenoproteins, which resulted in enhanced GPx antioxidant capacity, reduced ROS production, and decreased oxidative stress in tissues [17].

In contrast with previous research on ASD mice model that selenium can improve oxidative stress ASD significantly [17]. The study explained that selenium can improve ASD through the improvement of oxidative stress but also through inflammatory status in ASD mice model [17]. Thus, decreased oxidative stress may contribute to the decrease of ASD severity in that study.

This study has limitations, with selenium serum levels in ASD children were not identified.

We only used total Glutathione peroxidase (GPx) not specify in plasma (GPx-3) and in serum erythrocytes (GPx-1) are commonly used biomarkers for selenium adequacy supply.

Conclusions

Selenium could not increase the GPx serum level significantly. Giving selenium can help to decrease oxidative stress.

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