Effect of Selenium Micronutrient on Inflammatory Status in Autism Spectrum Disorder Children: A Randomized Control Trial

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Effect of Selenium Micronutrient on Inflammatory Status in Autism Spectrum Disorder Children: A Randomized Control Trial

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Abstract

Background: Autism spectrum disorder (ASD) children are characterized by increased proinflammatory agents. Previous studies found that administration of selenium can reduce inflammation; however, those studies were conducted on ASD mice model, and no study was conducted on the ASD patients. It is suspected that selenium could improve the development of ASD children by decreasing inflammation.

Aim: The present study aimed to evaluate the effect of selenium on inflammatory status in ASD children.

Method: This study was a randomized control trial. A total of 66 ASD children were selected and were randomly allocated to the first selenium intervention group (n=22), second selenium intervention group (n=22), and group control (n=22). Selenium as functional food and supplement was given to the intervention group for three months. The inflammatory state was measured by IL-1β, IL-6, and TNF-α serum. The ASD severity was measured by the autism treatment evaluation checklist (ATEC). Moreover, the intention-to-treat analysis was used in this study. The Wilcoxon test was used to compare before and after the intervention and Kruskal-Wallis test to compare the changes after the intervention.

Results: Based on findings of the present research, some insignificant changes in IL-1β, IL-6, and TNF-α were observed in the selenium intervention and control groups. The selenium intervention groups experienced a significant decrease in ATEC scores compared to the control group ($P<0.05$).

Implications for Practice: Although selenium did not decrease inflammatory status in ASD children, it could decrease the ASD severity. Appropriate interventions are needed to improve the inflammation in ASD children.

Keywords: Autism spectrum disorder, Inflammatory status, Micronutrients, Selenium

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Introduction

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by impairments in social interaction, communication, and repetitive behavior (1). Signs of neurodevelopmental disorders in ASD can be found since childhood (1–3). Prevalence of ASD is predicted to increase every year (4). There are around 0.6-1% children with ASD in the world, with the highest prevalence in Australia and the lowest in Asia (5,6). Autism spectrum disorder is more common in boys. Various disorders place a great burden on families and governments in terms of ASD's care (6).

The main part of the ASD's care is the appropriate nourishment and patient's nutritional status improvement (7,8). Appropriate nutrition is vital for healthy growth, healthy body structure, strength of immune system, as well as cognitive and neurological developments (9). However, some parents have poor attitude towards food security due to limited knowledge (10). A careful monitoring of the positive or negative outcomes pertinent to the nutrition diet and supplement of ASD children is required (8). Adopting diets which are tailored to ASD symptoms, is linked to the nutritional requirements and food preferences of the patients (7).

The ASD symptoms are believed to be related to the dysregulation of the immune system, although the exact underlying mechanism is not clear and remains controversial. Dysregulation of the immune system is believed to play a role in the ASD neurodevelopmental disorders; however, the exact underlying mechanism is unclear and controversial (11). A previous study has shown that developmental disorders in ASD children are associated with brain inflammation (12). The inflammation of the brain can occur due to early infection in the early days of the child's life or due to the influence of infection during pregnancy (13).

Microglia are the most abundant immune cells in the brain belonging to the innate immune system and represent 80% of the total brain immune cells (14). These microglia function to block the entry of infectious agents as they cross the blood-brain barrier, collect damaged cells and play a role in synapses of the central nervous system (15). Activation of microglia is associated with the upregulation of cytokines, which trigger immune responses (16). Cytokines are part of the immune system that functions to modulate a person's response to infection, injury, and inflammation (17). Inflammation is a body defence mechanism and is often linked to immune system dysfunction (18,19). Cytokines play a major role in modulating neural differentiation and plasticity in the central nervous system (20).

Previous studies found signs of activation of microglia and increased levels of cytokines, such as IL-6, TNF-α, Il-1β serum, brain, and cerebrospinal fluid in ASD children (15,19,21,22). The IL-6, TNF-α, and Il-1β will go to the brain through blood circulation, resulting in decreased brain function (19). The IL-6, TNF-α, and Il-1β were the most involved proinflammatory agents in ASD (17). The TNF-α which is mainly produced by mast cells and activated monocytes or macrophages can regulate immune cells through the production of IL-6, under the control of IL-1β (17). The higher the IL-1β, the higher the IL-6 (22). Levels of IL-1β, TNF-α, and IL-6 are glycoproteins whose presence in the brain must be in normal or low amounts, their high levels trigger neuroinflammation (22). Therefore, ASD manifestation may be related to the immune system due to strong inflammation found in ASD (17,21,22). This strong inflammation could be demonstrated by the examination of these cytokine biomarkers (19). As a result, dysregulation of these cytokines is responsible for the pathogenesis and severity of ASD (23). Studies found indications that certain cytokines can impair neurodevelopmental and behavioral disorders in ASD children (15,21). The ASD mice model with increased IL-6 showed impaired cognitive ability, decreased learning ability and social interaction, and anxiety (21). Increased IL-6 alters the formation of both excitatory and inhibitory synapses, disrupts the balance of excitatory and inhibitory synaptic transmission, and leads to behavioral disturbances (21). The IL-1β has a primary role in the initiation of local and systemic inflammatory processes and mediates the occurrence of neurodevelopmental abnormalities (24).

Inflammation in ASD children is thought to be related to a decrease in selenium levels (25). Several studies explain that selenium can improve adaptive and innate immunity (26). A previous study, in a mouse model of ASD, indicated that administration of selenium could significantly decrease proinflammatory agents, such as IL-1β, IL-6, and TNF-α (27). The results of the mentioned study also showed an improvement in social function, behavior, and cognitive function of the ASD mice model (27).

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Selenium is one of the micronutrients that the body needs in a certain amount which is useful to help maintain brain function, as well as plays a role in the immune system (26,28). Selenium is a micronutrient that could be obtained from various foodstuffs (e.g., fruit, meat, and beef liver) (29). Selenium can also be obtained in supplement forms. Selenium binds to proteins in the form of selenoproteins and is highly metabolized in the brain (30). So far, no research has been conducted to examine the effect of selenium administration on inflammatory status in ASD children (27). This research is the first study to evaluate the effective administration of selenium on the inflammatory status of ASD children as measured by IL-1β, IL-6, and TNF-α.

Methods

The design of the study was randomized controlled trial. A total of 66 participants were selected and using block randomization were randomly allocated at the beginning of the study into three groups of intervention group 1 (n=22), intervention group 2 (n=22), and control group (n=22). Moreover, simple random sampling was used. The sample size was estimated based on a study by Adams et al. (31). It was estimated that minimum of 22 participants in each group would provide 80% power to detect a 20 score difference in the scale, with ά =0.05, allow a 10% drop- out rate. Participants were recruited from 14 different autistic clinics in East Java, Indonesia. All participants were ASD diagnosed by a pediatrician at the clinic. Inclusion criterion was participants of 2-6 years of age. Children with Bel Palsy, heart disorders, and mental disorders were excluded from the study.

The inflammatory state was analyzed by examining the IL-1β, IL-6, and TNF-α serum levels in the laboratory. The laboratory officer was blind to the process, before and three months after the intervention. Analysis of IL-1β, IL-6, and TNF-α was performed using enzyme-linked immunosorbent assay method. The IL-1β, IL-6, and TNF-α serum levels were expressed as nanogram per litre (ng/L). In addition, the ASD progression was assessed. The ASD progression was assessed using the autism treatment evaluation checklist (ATEC), which is a valid and reliable tool. For test-retest analyses, a correlation co-efficient value more than 0.9 was found for all subscales and in total, indicating that the ATEC is reliable. For the concurrent validity, a correlation coefficient of 0.8 (P<0.001) was measured, indicating the high validity of this tool (32). The ATEC is a commonly used instrument to evaluate the effectiveness of a given therapy or intervention in the development of ASD (33). Demographics, such as age and gender were assessed in this study.

Intervention groups were given selenium. The first intervention group was given selenium supplement in powder form with a dose of 1 x 20 g/day, while the second intervention group was given selenium in the form of selenium-containing functional food from a cow's heart with a dose of 50 g/day. The mocap flour which was roasted for 15 min at a dose of 1 x 30 g/day was given to the control group. The packaging of selenium supplements and mocap flour was done by pharmacists at pharmacies who were accredited with Good Pharmacy Practice in the same powder and packaging. The participants in the second intervention group did not know that the functional food provided by nutritionist were high in selenium. The nutritionist gave the food to the participants' parents and their parents gave the food to them. The participants in the first intervention group and control group did not know whether the capsules given to them by pharmacists contained selenium or not. The intervention was carried out for three months.

Intention-to-treat analysis was used in this study. Data analysis was performed using IBM SPPS (version 25). Kolmogorov-Smirnov test was performed to determine the normality of distribution from continuous variables. The collected data displayed through mean ± standard deviation. Comparison of the groups before and after the intervention was performed using Wilcoxon test and the change after the intervention were compared between groups using a Kruskal-Wallis test.

Results

Sixty-six ASD children were included in this study. One ASD child due to personal reasons left in the middle of the study (Figure 1). Therefore, we used the intention-to-treat analysis, and the obtained results were used to predict the rest of the participant's data. All three groups had homogeneous ages, sex, and ATEC score at baseline (Table 1). There was no difference in IL-1β, IL-6, and TNF-α levels before and after the intervention in the control and intervention groups [P>0.05; Table 2]. No significant difference was observed in IL-1β, IL-6, and TNF-α changes after three months of the intervention between the three groups [P>0.05; Table 3].

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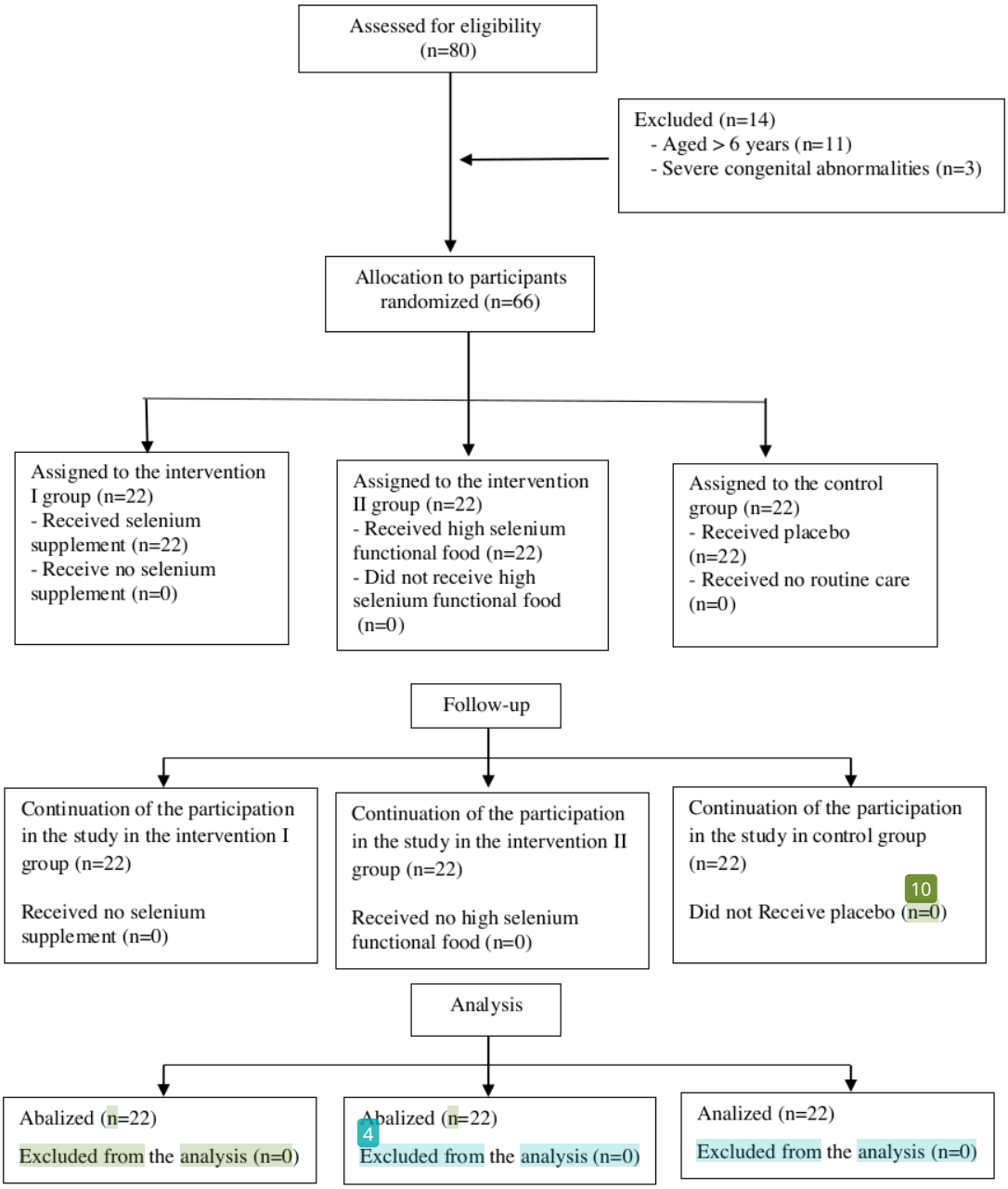

Figure 1. Consort diagram of the study

Table 1. Characteristics of the participants

Characteristics	Intervention group (1) (n=22)	Intervention group (2) (n=22)	Control group (n=22)	*P*-value
Age (Year)	3.90±0.97	3.95±1.43	3.77±1.34	0.840*
Gender				
Male	19(86.36%)	19(86.36%)	20 (90.90%)	0.867**
Female	3(13.64%)	3(13.64%)	2(9.10%)	
ATEC	97.72±20.54	96.68±13.88	95.50±20.53	0.924***

*Kruskal-Wallis test, ** Chi-Square test, ***One-way ANOVA , ATEC: Autism treatment evaluation checklist

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Table 2. Inflammation status and autism treatment evaluation checklist score before and after the intervention

Inflammation status	Intervention group (1)	Intervention group (2)	Control group
IL-1β (ng/L)			
Before	80.75±67.76	68.08±61,97	116.46±85.75
After	71.87±84.85	89.80±99,93	93.89±77.24
P	0.249*	0.783*	0.223*
IL-6 (ng/L)			
Before	146.57±160.98	263.47±256.69	232.41±166.71
After	170.57±144,08	224.67±153.97	201.17±148.78
P	0.390*	0.638*	0.733*
TNF-α (ng/L)			
Before	116.36±159.66	70.47±52.54	115.52±80.80
After	83.39±82.39	93.55±81.07	118.63±70.54
P	0.355*	0.322*	0.783*
ATEC Score			
Before	97.72±20.54	96.68±13.88	95.50±20.53
After	42.95±13.51	76.40±15.21	87.86±19.89
P	<0.001**	<0.001**	<0.001**

*Wilcoxon test, ** Paired t-test, ATEC: Autism treatment evaluation checklist

Table 3. Changes after three months

	Intervention group (1)	Intervention group (2)	Control group	*P*
IL-1β	-8.87±7.98	21.79±8.33	-22.57±7.43	0.366
IL-6	23.99±16.96	-38.80±24.98	-31.23±16.56	0.683
TNF-α	-26.96±23.08	23.08±7.59	3.10±7.93	0.386
ATEC score	-54.77±7.03	-20.28±1.33	-7.63±4.45	<0.001

Kruskal-Wallis test, ATEC: Autism treatment evaluation checklist

Discussion

The present study aimed to evaluate the effect of selenium administration on the inflammatory status of ASD children. Based on findings of the present research, insignificant changes were observed in serum levels of IL-1β, IL-6, and TNF-α in the selenium intervention groups. The IL-1β and TNF-α levels were decreased in ASD children who were given selenium in the form of functional food, while the IL-6 level was decreased in ASD children who were given selenium supplements. However, the same result was observed in children who were not given selenium with the groups given selenium supplements. Inflammation status in the three groups showed no significant change. This inflammation status can be demonstrated by examining these cytokine biomarkers in ASD (19).

The IL-1β, IL-6, and TNF-α are the family of cytokines that are mostly involved in ASD (19). The IL-1β is a small multifunctional cytokine/protein that is released from many tissues, including white blood cells, endothelial cells, epithelial cells, adipose tissue, astrocytes, microglia, and neurons (22,34). The IL-1β and IL-6 pleiotropic cytokines are involved in almost every organ (22,34). The IL-6 functions in nonspecific and specific immunity produced by mononuclear phagocytes, vascular endothelial cells, fibroblasts, and other cells, in response to microbes and other cytokines (22,34). The TNF-α is a major cytokine in the acute inflammatory response to gram-negative bacteria and other microbes (22,34). Furthermore, TNF-α is an immune response of cytokines, produced by activated macrophages, which the main function of TNF-α is to increase the activation and production of acute phase proteins (19,21).

This study analyzed IL-6, TNF-α, and Il-1β serum in ASD children before and three months after the intervention. Previous studies found increased levels of IL-6, TNF-α, and Il-1β serum in ASD children (15,19,21,22). The IL-6, TNF-α, and Il-1β will go to the brain through blood circulation, resulting in decreased brain function (19). The ASD manifestation is related to the immune system due to the strong inflammation found in ASD (17,21,22). Dysregulation of these cytokines is responsible for the ASD pathogenesis and severity (23). Studies revealed that certain cytokines can impair neurodevelopmental and behavioral disorders in ASD children (17,19). The ASD mice model with increased IL-6 showed impaired cognitive ability, decreased learning ability and social interaction, and anxiety (21). Increased IL-6 alters the formation of both excitatory and inhibitory

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synapses, disrupts the balance of excitatory and inhibitory synaptic transmission, and leads to behavioral disturbances (27). The IL-1β plays a key role in the initiation of local and systemic inflammatory processes, and mediates the occurrence of neurodevelopmental abnormalities (24). Therefore, the higher IL-1β leads to higher IL-6 (22).

The findings of the present study is not in line with previous studies which explained that the administration of selenium will reduce the inflammatory status in ASD mice model, which are characterized by improvements in the three serum levels (27). However, the results of the ASD severity examination in the three groups after three months of intervention showed a significant improvement. The ASD children who were given selenium either in the form of functional foods or selenium supplements experienced a better reduction in ATEC scores than the control group. These changes suggest that selenium can improve ASD, although cannot improve the inflammation status. Regarding the previous research on ASD mice model that selenium can improve ASD (27), it was explained that ASD could be improved by selenium, not only through the improvement of oxidative stress, but also through inflammatory status in ASD mice model (27). Consequently, decreased oxidative stress may contribute to the decrease of ASD severity in this study. In addition, although proinflammatory levels insignificantly decreased, ASD improvement still occured. This study has limitations, with selenium serum levels in ASD children were not identified. Glutathione peroxidase (GPx) in plasma (GPx-3) and in serum erythrocytes (GPx-1) are commonly used as biomarkers for selenium adequacy supply. This study did not examine GPx-1 and GPx-3; therefore, the adequacy of selenium in ASD children is not known. This could explain that selenium inadequacy in ASD children could not affect the inflammatory status.

Implications for practice

Although selenium did not improve the inflammation status of children with ASD, it can improve the severity of ASD. Administration of selenium could be used as an intervention to improve the quality of care for ASD patients. The appropriate intervention is needed to improve inflammation status in ASD children.

Acknowledgments

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Conflicts of interest

The authors declared no conflict of interest.

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