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The Administration of Omega-3 Therapy on C-Reactive Protein Levels, Neutrophil-To-Lymphocyte Ratio, Malondialdehyde, and Glasgow Outcome Scale Extended Scores in Patients with Moderate to Severe Head Injuries at Prof. Dr. I.G.N.G. Ngoerah General Hospital Denpasar

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ABSTRACT

Head injury is one of the most common causes of death worldwide and also the most frequent cause of lifelong disability. Mechanically, several factors contribute to secondary injury, including neuroinflammation, excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, axonal degeneration, and apoptotic cell death. The fundamental principle in managing head injury is to create an optimal environment for the injured brain tissue to recover and regain normal function. Omega-3, as an adjunct therapy for head injury patients, has anti-inflammatory effects and is effective as a strong anti-inflammatory factor. This study compares the administration of omega 3 as an adjunct therapy and standard therapy in terms of CRP, NLR, MDA levels, and GOS-E scores in patients with moderate and severe head injuries. Sample selection used a consecutive sampling technique, followed by simple randomization. In this study, normality testing was conducted using the Shapiro-Wilk test and median differences were analyzed using the Mann-Whitney test. The results show that omega-3 administration resulted in lower CRP ($p < 0.001$), NLR (p 0.015), and MDA (p 0.001) levels in patients with moderate to severe head injuries, but provided the same GOS-E scores as the control group (p 0.717).

Keywords: head injury; omega 3; CRP; NLR; MDA; GOS-E.

INTRODUCTION

Head injuries remain a significant issue for society and for healthcare providers and policymakers. The consequences include disability, mortality, and substantial financial burdens for patients and their families. The most vulnerable group to head injuries is young individuals in their productive age. Addressing head injuries also requires considerable resources, which are costly for both central and local governments. Head injuries in the United States affect approximately 1.7 million individuals annually, with the highest prevalence observed among individuals aged 15 to 19 years and those above 65 years. The incidence rate of traumatic brain injuries (TBIs) is around 500 cases per 100,000 people per year. The frontal and temporal lobes of the brain are the areas most commonly affected [1].

According to the Riset Kesehatan Dasar 2018 (RISKESDAS) report, the prevalence of head injuries in Indonesia reached 11.9%, ranking third after injuries to the lower limbs (67.9%) and upper limbs (32.7%). The age groups most frequently affected by head injuries are individuals over 65 years old (17.1% prevalence), followed by those aged 45–54 years (10.6%) and 35–44 years (10.1%)[2].

Most head injuries are reported to occur at home and in patients' surroundings, particularly in traffic accidents. Head injuries are a leading cause of death globally and a primary cause of lifelong disability [3].

The Brain Injury Association of America defines a head injury as damage caused by external mechanical forces affecting the cranial and intracranial structures, leading to either temporary or permanent brain damage [4]. The pathological process of head injuries is highly complex, involving cellular and molecular pathways. Head injuries are generally classified into primary and secondary injuries [5]. Primary head injuries refer to immediate damage to the scalp, skull, brain tissue (neurons, axons, and glial cells), and cerebral blood vessels caused by cranial trauma. These injuries result in irreversible nerve damage. With mild trauma and appropriate therapy, the brain may recover to normal function. However, in cases of severe trauma or inadequate therapy, primary head injuries can progress to more severe secondary head injuries [6]. The neuroinflammatory process during the first 24 hours after acute head trauma disrupts the blood-brain barrier, leading to the infiltration of circulating neutrophils, monocytes, and lymphocytes into the injured brain parenchyma [7].

Inflammation is commonly assessed using C-reactive protein (CRP) levels and the neutrophil-to-lymphocyte ratio (NLR). In head injury patients, CRP levels in the blood are significantly correlated with systemic inflammatory response syndrome (SIRS). CRP levels typically increase within the first two weeks after injury and are directly proportional to the severity of the injury [8]. Elevated NLR values in head injury patients are associated with poor prognoses [9]. Research indicates that inflammatory markers such as CRP and NLR play significant roles in the inflammatory process following traumatic brain injuries [10].

Increased levels of reactive oxygen species (ROS) can trigger the formation of hydrogen peroxide. Malondialdehyde (MDA), a prominent aldehyde derivative, reflects the extent of oxidative stress and free radical activity in the body. MDA exhibits toxic effects by damaging cellular membranes. The fundamental principle of head injury management is to create an optimal environment for the recovery and normal functioning of injured neural tissues. Treatment approaches include external decompression (decompressive craniectomy with hematoma evacuation) and internal interventions (head elevation, oxygenation, hyperosmolar therapy, antiepileptic therapy, supportive care, and neuroprotective agents) [11]. Omega-3 fatty acids have been identified as a supportive therapy for traumatic brain injury due to their accessibility and affordability. Omega-3 fatty acids are essential nutrients that cannot be synthesized by the body and are integral components of cell membranes. They influence cell receptor function and consist of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which possess anti-inflammatory properties, reduce apoptosis, mitigate oxidative stress, and improve mitochondrial dysfunction. Additionally, Omega-3 fatty acids enhance antioxidant enzyme activity, reduce excitotoxicity, and modulate calcium and potassium channels critical for neuroprotection [12]. Based on this background, a study was conducted to investigate the effects of Omega-3 therapy on reducing CRP, NLR, and MDA levels and improving Glasgow Outcome Scale-Extended (GOS-E) scores in patients with moderate to severe head injuries at Prof. Dr. I.G.N.G. Ngoerah General Hospital in Denpasar.

METHODS

Study Population and Design

This study was conducted over six months, from January 2024 to July 2024, involving all patients with moderate to severe head injuries treated at Prof. Dr. I.G.N.G. Ngoerah General Hospital in Denpasar. This study employed a pure experimental design using a randomized controlled trial (RCT) approach. Samples needed for this study were 46 samples, divided into two groups (treatment and control) using a simple randomization technique. It compared two groups: the treatment group (receiving additional Omega-3 therapy) and the control group (receiving standard therapy). Subject allocation to either the treatment or control group was randomized, and the subjects were blinded to their group assignment. Dependent variables (CRP, NLR, MDA, and GOS-E) were measured for each subject. CRP, NLR, and MDA levels were assessed twice: on the first day of hospital admission and on the seventh day of treatment. The outcome variable, GOS-E score, was measured three months after the intervention.

The research protocol and informed consent in this study were approved by the Research Ethics Committee, Faculty of Medicine, Universitas Udayana (1870/UN14.2.2.VII.14/LT/2024). All data and information of patients were used for research only and followed the principle of privacy. Patients meeting these criteria were included: all patients aged 18-70 years with moderate to severe head injuries. Subjects meeting any of the following were excluded: Patients with multiple trauma, sustained injuries due to a prior stroke influence of intoxication, which may obscure consciousness assessment during examination, pregnant patients, who passed away before the seventh day of hospitalization, and declined to participate in the study after being provided with informed consent.

Statistical Analysis

All statistical analysis was done using SPSS 25.0. The study included a total of 46 samples, and the Shapiro-Wilk test was used for normality testing. Median comparison analysis was conducted to evaluate CRP, NLR, MDA levels, and GOS-E scores based on the treatment groups. The Mann-Whitney test was employed for median comparison, as the data distribution in both groups was non-normal.

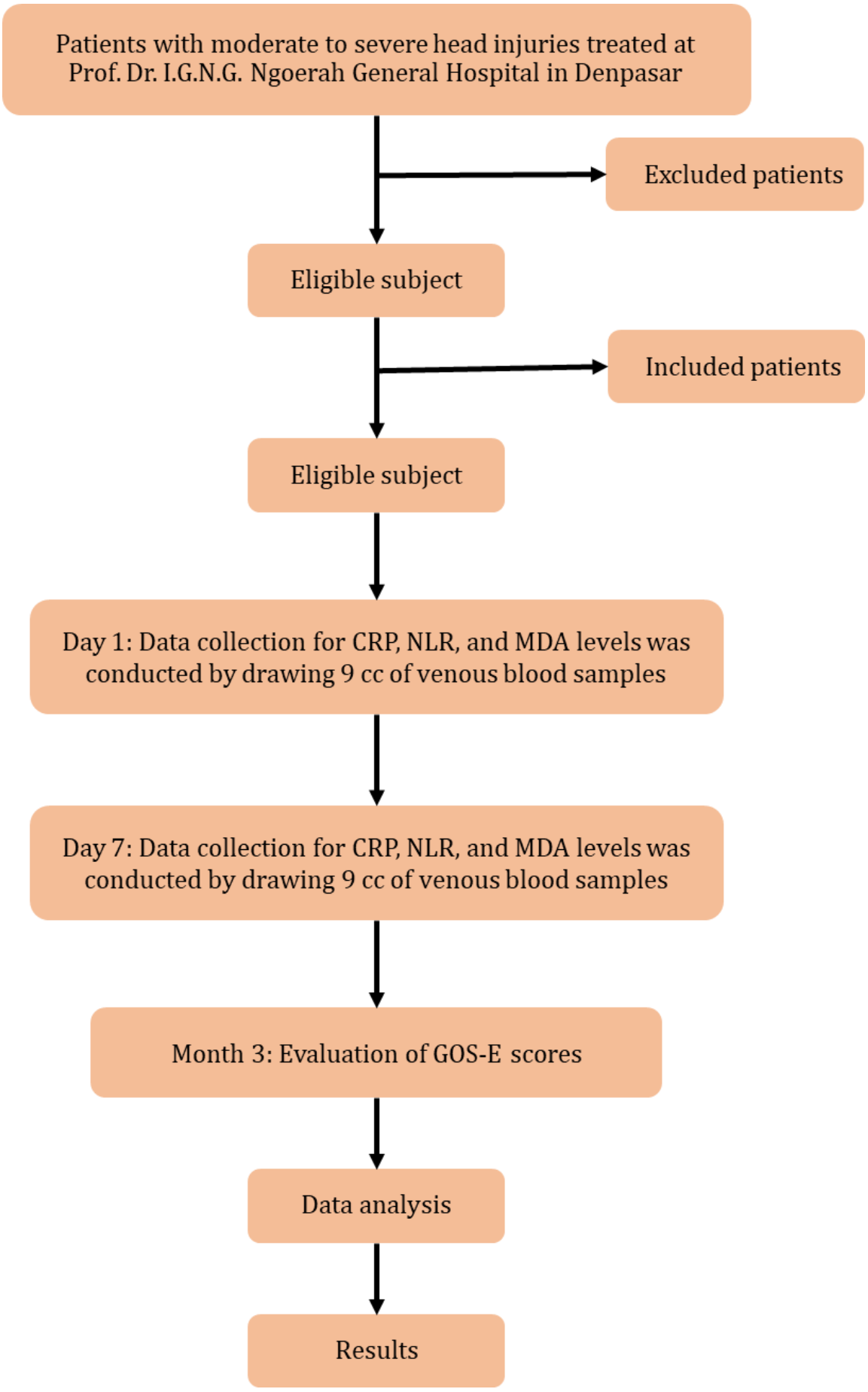

FIGURE 1: Study Flow Diagram.

RESULTS

Patients Characteristics

A total of 46 subjects were included in this study. All study subjects were patients with moderate to severe head injuries treated at Prof. Dr. I.G.N.G. Ngoerah General Hospital.

The subjects comprised 23 patients in the treatment group who received Omega-3 therapy and 23 patients in the control group who did not receive the therapy.

TABLE 1: Patient Characteristics.

Characteristics		Treatment	Control
Age	Median (IQR)	45 (30)	40 (27)
Sex			
Male	N (%)	13 (56,5)	16 (69,6)
Female	N (%)	10 (43,5)	7 (30,4)
GCS	Median (IQR)	10 (5)	10 (5)
CRP	Median (IQR)	89,0 (55,8)	95,2 (34,3)
NLR	Median (IQR)	9,9 (9,6)	10,0 (11,5)
MDA	Median (IQR)	9,8 (5,1)	10,5 (4,3)
GOS-E score	Median (IQR)	7 (2)	7 (3)

The Effect of Additional Omega-3 Therapy on CRP Levels in the Treatment and Control Groups

The comparison of CRP data between the treatment and control groups was performed using the Mann-Whitney test. This analysis was used to assess CRP levels on Day 1 and Day 7 in both the treatment and control groups.

The results of this non-parametric test revealed a significant difference in CRP levels between Day 1 and Day 7 in both the treatment and control groups ($p < 0.001$).

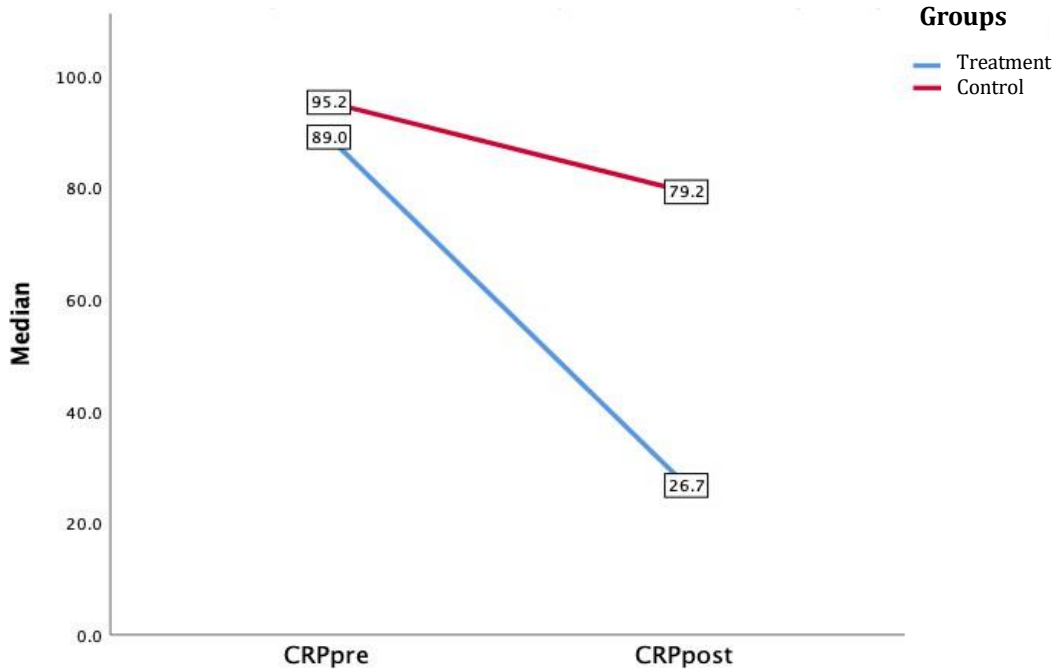

FIGURE 2: The Difference in CRP Variables Between the Treatment and Control Groups.

The Effect of Additional Omega-3 Therapy on NLR Levels in the Treatment and Control Groups

The comparison of NLR data between the treatment and control groups was performed using the Mann-Whitney test. This analysis was used to assess NLR levels on Day 1 and Day 7 in both the treatment and control groups.

The results of this non-parametric test revealed a significant difference in NLR levels between Day 1 and Day 7 in both the treatment and control groups ($p = 0.015$).

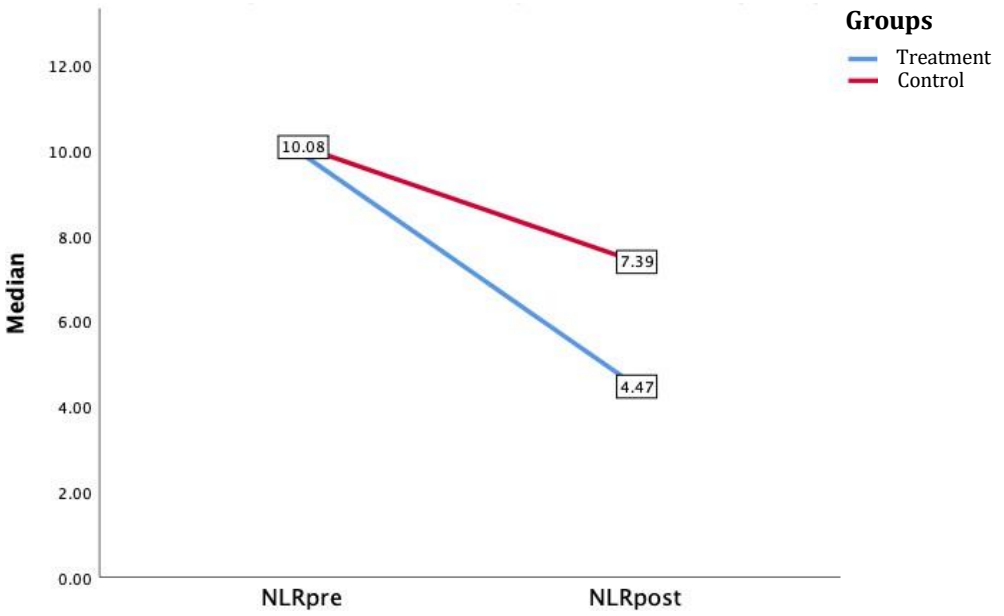

FIGURE 3: The Difference in NLR Variables Between the Treatment and Control Groups.

The Effect of Additional Omega-3 Therapy on MDA Levels in the Treatment and Control Groups

The comparison of MDA data between the treatment and control groups was performed using the Mann-Whitney test. This analysis was used to assess MDA levels on Day 1 and Day 7 in both the treatment and control groups. The results of this non-parametric test revealed a significant difference in MDA levels between Day 1 and Day 7 in both the treatment and control groups ($p = 0.001$).

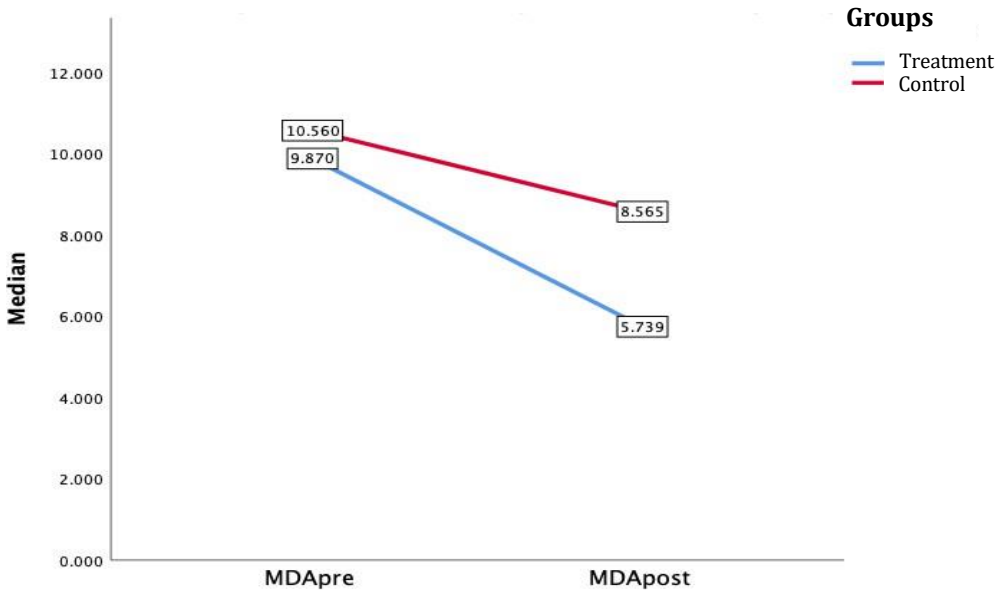

FIGURE 4: The Difference in MDA Variables Between the Treatment and Control Groups.

The Effect of Additional Omega-3 Therapy on GOS-E Scores in the Treatment and Control Groups

The GOS-E score variable was analyzed using the Mann-Whitney test due to non-normal data distribution in the normality test. It was found that there was no significant difference in GOS-E scores between the treatment and control groups ($p = 0.717$).

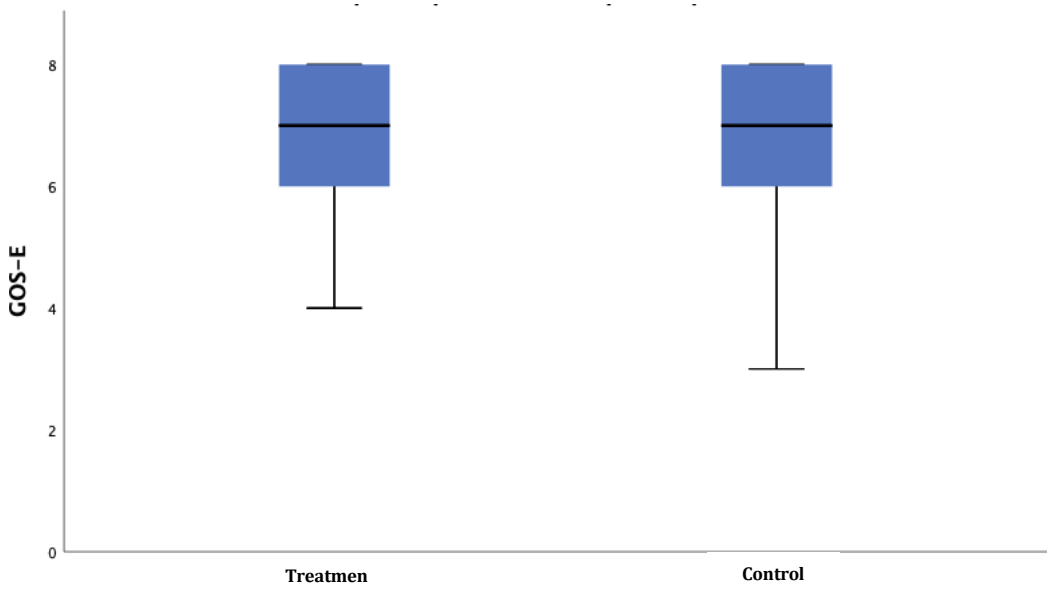

FIGURE 4: The Difference in GOS-E Scores Between the Treatment and Control Groups.

DISCUSSION

The study involved 46 subjects, consisting of 23 patients who received additional Omega-3 therapy (treatment group) and 23 patients who received standard therapy (control group). The study sample was predominantly male, with 29 male patients and a median age of 45 years in the treatment group and 40 years in the control group. The primary cause of head injury was traffic accidents, with the highest GCS score being 13 and the lowest being 5 at the time of admission.

Head injury is defined as brain tissue damage caused by external forces to the cranium, which may extend to the intracranial structures, resulting in both temporary and permanent effects [4]. Primary head injury refers to the direct effects of mechanical disturbances on the brain, leading to two types of injury: focal and diffuse. Secondary head injury is a continuation of primary injury due to pathological conditions that lead to a decline in cerebral function, caused by extracranial factors. Factors contributing to secondary injury include neuroinflammation, excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, axonal degeneration, and apoptosis [13]. According to Riskesdas 2018, the proportion of head injuries in Indonesia is 11.9%, ranking third after injuries to the lower and upper limbs. Individuals aged 25-64 years, which includes the productive age range, are the most affected by head injuries. Males have a higher incidence of head injuries compared to females due to their higher productivity levels. This is consistent with the findings of this study, which showed a median age of 40 years in the control group and 45 years in the treatment group, with more males than females [2].

CRP is a non-specific, sensitive systemic inflammatory biomarker that increases in response to various conditions, including head injury. The synthesis of CRP is induced by IL6 and is further increased by IL1b and TNF-α, which are pro-inflammatory molecules [14].

Nuclear Factor Kappa B (NFkB) is a gene involved in the secretion of various cytokines, including TNF-α. Activation of NFkB leads to increased expression of TNF-α, which subsequently activates IkB protein kinase, causing dissociation of the NFkB complex. This process results in decreased expression of adhesion molecules and reduced production of inflammatory cytokines through the COX-2 pathway. A drastic increase in CRP levels is commonly found in conditions such as spontaneous intracerebral hemorrhage, trauma, and degenerative diseases like Alzheimer's [15].

In this study, a significant reduction in CRP levels was observed in the treatment group receiving additional Omega-3 therapy compared to the control group. This suggests that Omega-3 administration in patients with moderate and severe head injuries reduces the inflammation process. These findings are consistent with studies by Elisia et al. and Wiyarta et al., which show that Omega-3 can significantly lower CRP levels due to its EPA and DHA content, which act as anti-inflammatory agents to inhibit NFkB (nuclear factor kappa-light- chain-enhancer of activated B cells) activity. Animal and human studies have shown that the intake of omega-3 fatty acids decreases the production of TNF-α, IL-1, and IL-6. Inhibited NFkB activity leads to decreased secretion of CRP [15].

The Omega-3 content, especially the fatty acids EPA and DHA, has a significant ability to lower CRP levels due to their anti-inflammatory effects. One of the main mechanisms behind this effect is the activation of peroxisome proliferator-activated receptor (PPAR-γ) by Omega-3. PPAR-γ is a transcription factor involved in regulating genes involved in inflammation. When PPAR-γ is activated, it inhibits NFkB activity, a transcription factor that controls the expression of pro-inflammatory genes. By inhibiting NFkB, Omega-3 helps reduce the production of inflammatory cytokines like TNF-α, IL-1, and IL-6, which in turn lowers CRP levels in the blood [15].

Neutrophils are a key component of the innate immune system, playing an important role in the inflammatory process by fighting pathogens, but they can also cause widespread tissue damage. Pathological conditions such as trauma, bleeding, ischemia, and infection can lead to an increase in neutrophils infiltrating brain tissue. Elevated neutrophil levels trigger an inflammatory response by releasing various chemokines and molecules that affect oxidative activity, leading to secondary damage to local and surrounding tissues. Head injury results in an increase in neutrophils and a decrease in lymphocytes. This causes an increase in the neutrophil-lymphocyte ratio (NLR), which reflects the severity of neuroinflammation, blood-brain barrier disruption, edema, cerebral hypoxia, oxidative stress, and cell damage (apoptosis/necrosis). This inflammatory process indicates that the higher the NLR, the more severe the degree of secondary head injury [10].

The NLR is also inversely correlated with the Omega-3 Index, which indicates the levels of EPA and DHA in the blood. Studies have shown that an Omega-3 Index of <6.6% is associated with higher NLR. The relationship between NLR and head injury outcomes is being increasingly studied as a prognostic factor. Omega-3 supplementation has been shown to reduce inflammatory factors and NLR, suggesting it may improve outcomes in head injury patients [16].

Metabolites derived from Omega-3 play an important role in immune regulation. These metabolites, generally known as pro-resolving mediators, can be classified into several families, including prostaglandins, leukotrienes, thromboxanes, maresins, protectins, and resolvins. Their synthesis is regulated by enzymes such as cyclooxygenase, lipoxygenase, or cytochrome P450. Omega-3 and Omega-6 substrates compete for these enzymes, as well as for elongases and elastases. Thus, the presence of Omega-3 fatty acids reduces the synthesis of Omega-6-derived metabolites, which also have effects on immune cells. This competition represents an additional level of immune regulation by Omega-3 fatty acids. Although the specific mechanisms by which Omega-3 fatty acids regulate immune cell functions exhibit some characteristics depending on the cell type, it is important to note that Omega-3 fatty acids, through in vitro stimulation or food supplementation, effectively integrate into the cell membranes of all immune cells studied thus far. Polyunsaturated fatty acids contain several double bonds in their carbon chain, which cause bends in the chain. Because of these bends, polyunsaturated fatty acids cannot pack as tightly in cell membranes as saturated fatty acids. Therefore, the incorporation of polyunsaturated fatty acids increases membrane fluidity [10]. Previous studies have reported that fish oil supplementation with Omega-3 content was evaluated for its effects on neutrophil migration capacity. Fish oil supplementation was found to increase neutrophil migration capacity. However, it was also reported that by lowering pro-inflammatory eicosanoid levels, Omega-3 reduces systemic inflammation often observed in head injury patients, thereby decreasing NLR [17]. Secondly, Omega-3 can also influence the function and activity of immune cells, particularly neutrophils and lymphocytes. Omega-3 helps stabilize cell membranes, enhance lymphocyte function, and reduce excessive neutrophil activation. Overactive neutrophils can cause further tissue damage and increase the inflammatory response. By regulating these cell activities, Omega-3 helps balance the ratio of neutrophils to lymphocytes, thereby lowering NLR. Thirdly, Omega-3 plays a role in tissue repair and recovery after injury. Omega-3 supports cell and tissue regeneration by improving the structure of cell membranes and increasing blood flow to the injured area. Increased blood flow and nutrition to the injury site contribute to reducing local and systemic inflammation, which in turn can lower NLR. Omega-3 polyunsaturated fatty acids (n-3 PUFAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) play a critical role in nerve cell function, neurotransmission, and inflammatory and immune responses involved in neuropsychiatric disease conditions. A large body of experimental and epidemiological studies provides a strong basis for interventional clinical trials evaluating the clinical efficacy of n-3 PUFAs in various neurological and psychiatric disorders. Most of these trials have found beneficial effects of food supplementation with EPA and DHA, with no significant safety concerns [18].

MDA levels are the final products of lipid peroxidation, generated from the peroxidation of polyunsaturated fatty acids, and serve as markers for lipid peroxidation and oxidative damage. The MDA concentration is influenced by the number of free radicals in the body, which triggers lipid peroxidation and the production of arachidonic acid, initiating DNA-damaging agents such as MDA and 4-HNE. MDA levels have a toxic effect that damages cell membranes due to oxidative stress. Omega-3 (EPA and DHA) is a bioactive compound that can synergistically counteract lipid peroxidation and enhance endothelial function. Omega-3 is an essential fatty acid that cannot be synthesized by the body and must be obtained from external sources. Omega-3 helps reduce MDA levels, thereby providing antioxidant protection against reactive oxygen species [19].

In this study, a significant reduction in MDA levels was observed in the treatment group that received additional Omega-3 therapy compared to the control group. These results are consistent with the theory and previous research indicating that Omega-3 can lower MDA levels in patients with mild and severe head injuries. The mechanism by which additional Omega-3 therapy lowers MDA levels in patients with mild and severe head injuries involves several important aspects of body physiology and biochemistry. Omega-3, found in fish and fish oil supplements, is an essential fatty acid known for its anti-inflammatory and antioxidant effects. In head injuries, particularly severe ones, oxidative stress increases free radical production, including malondialdehyde, which causes further damage to brain cells and tissue [19].

Omega-3 plays a key role in reducing oxidative stress by enhancing antioxidant activity in the body. Omega-3 fatty acids like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can regulate the production and activity of antioxidant enzymes, which in turn helps reduce MDA concentrations. Research shows that Omega-3 can lower free radical production and enhance the body's ability to combat oxidative damage, thereby reducing MDA levels in the blood and tissue. In addition to its antioxidant effects, Omega-3 also has significant anti-inflammatory properties. Head injuries are often accompanied by excessive inflammation, which contributes to tissue damage and increased oxidative stress. Omega-3 can inhibit the production of inflammatory mediators such as prostaglandins and leukotrienes, which often worsen inflammatory conditions. By reducing inflammation, Omega-3 helps reduce cell and brain tissue damage, contributing to lower MDA levels (Poblete et al., 2024).

Overall, additional Omega-3 therapy provides significant benefits for patients with mild and severe head injuries by lowering MDA levels. By modulating oxidative and inflammatory processes, Omega-3 helps protect brain cells from further damage, supports recovery, and improves clinical outcomes. Further research could help optimize the dosage and duration of Omega-3 therapy for better outcomes in head injury contexts [20].

This study shows similar results between the GOS-E scores in both the treatment and control groups after a 3-month post-trauma evaluation. Recent studies indicate that, although there is theoretical support and some clinical evidence for the benefits of Omega-3 in post-head injury recovery, research findings often vary. Some studies show potential benefits, while others find no significant difference between the Omega-3 treatment and control groups. According to Hoffer et al., recent studies found that Omega-3 supplementation in patients with traumatic brain injury produced variable results, and the positive effects on the GOS-E score were not always statistically significant. They noted that therapeutic effects might be influenced by several factors, including the dose and duration of treatment [21]. Liu et al. (2024) conducted research on the effects of Omega-3 in patients with repeated head injuries and found that, although there were some improvements in biomarkers related to inflammation, the difference in GOS-E scores between the treatment and control groups was not significant after 3 months [22]. Another study conducted a systematic review of studies on Omega-3 and head injury, showing that Omega-3 reduces inflammation levels, which may reduce morbidity and mortality in patients [20]. A related study by Patel and Lee concluded that, although some studies suggest potential benefits, many do not find significant effects on long-term outcomes such as mortality. This indicates the need for further research to understand the role of Omega-3 in post-head injury therapy [23].

Omega-3 fatty acids have a strong anti-inflammatory effect, helping reduce brain tissue inflammation after injury. This reduction in inflammation contributes to nerve cell protection and accelerates brain recovery. In addition to their anti-inflammatory effects, Omega-3s are also involved in the formation and maintenance of healthy cell membranes. DHA, in particular, is a key component of neuronal cell membranes and plays a role in membrane fluidity and synaptic function. By increasing DHA levels in cell membranes, Omega-3 therapy can support neuron-to-neuron communication and enhance synaptic plasticity, which is vital for post-injury rehabilitation and cognitive function. This, in turn, may contribute to improved GOS-E scores by enhancing the cognitive and functional abilities of patients [23]. Supplementary therapy with Omega-3 also affects cellular signaling pathways associated with tissue repair and neuroprotection. For instance, Omega-3 can modulate signaling pathways such as the NFkB pathway, which regulates inflammatory responses and cell proliferation. By suppressing the activation of this pathway, Omega-3 helps reduce further cellular damage and promotes tissue repair and regeneration in the brain [21].

Therefore, Omega-3 plays a role in genetic modification and protein expression related to brain injury recovery. Omega-3 can influence the expression of genes related to oxidative stress responses and cellular repair. By regulating the expression of genes and proteins involved in these processes, Omega-3 can modulate the body's response to brain injury, reduce further damage, and support better functional recovery. With all these mechanisms working together, Omega-3 supplementation may improve GOS-E scores, reflecting better functional outcomes for patients with head injuries.

CONCLUSIONS

In conclusion, this study found that supplementary omega-3 therapy, compared to standard therapy, results in lower CRP, NLR, and MDA levels in patients with moderate to severe head injuries. In contrast, supplementary omega-3 therapy, compared to standard therapy, results in the same GOS-E scores in patients with moderate to severe head injuries.

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