Scientific Research Publishing

Food and Nutrition Sciences, 2020, 11, 887-898
https://www.scirp.org/journal/fns
ISSN Online: 2157-9458
ISSN Print: 2157-944X

Fatty Acid Treatment with Pure Omega-3 Eicosapentaenoic Acid Ethyl Ester for Patients with Cardiovascular Diseases: Differences between Branded (EPADEL®) and Generic Products

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How to cite this paper: Suwa, W., Morii, I. and Kino, M. (2020) Fatty Acid Treatment with Pure Omega-3 Eicosapentaenoic Acid Ethyl Ester for Patients with Cardiovascular Diseases: Differences between Branded (EPADEL®) and Generic Products. *Food and Nutrition Sciences*, **11**, 887-898.
https://doi.org/10.4236/fns.2020.1110062

Received: September 25, 2020
Accepted: October 12, 2020
Published: October 15, 2020

Abstract

Background: Omega-3 polyunsaturated fatty acids (PUFAs) have some protective benefits for patients with coronary artery and cerebrovascular diseases. Eicosapentaenoic acid (EPA) drugs are prescribed as branded (B: EPADEL®) or generic products but no data exist concerning the differences in treatment outcomes between these products. **Methods and Results:** We investigated the differences in the serum levels of EPA, docosahexaenoic acid (DHA) and arachidonic acid (AA), and the EPA/AA ratios through blood sampling six months after daily administration of 1800 mg of EPADEL® and a generic EPA drug was initiated for 96 patients with cardiovascular diseases. All patients received these PUFA treatments while continuing with baseline therapy. After 6 months of administration, EPADEL® produced better results than the generic (G) product (EPA; baseline: 59.4 ± 25.5 μg, B: 215.5 ± 58.8 μg, G: 199.7 ± 63.8 μg, B vs G, $p < 0.0005$; AA; baseline: 197.4 ± 44.6 μg, B: 158.3 ± 36.3 μg, G: 163.6 ± 38.9 μg, B vs G, $p < 0.02$, as mean ± SD). **Conclusions:** There were clear differences between EPA branded and the generic products. Further study is required to determine whether the benefits from the branded product justify the higher price compared to the generic drug cost.

Keywords

Eicosapentaenoic Acid (EPA), Arachidonic Acid (AA), Docosahexaenoic Acid (DHA), Omega-3 Polyunsaturated Fatty Acids, Branded Product, Generic Product

1. Introduction

The observational study in Greenland Eskimos had shown that they had high plasma level of eicosapentaenoic acid (EPA) and low plasma level of arachidonic acid (AA) and had a low incidence of myocardial infarction [1]. As the mechanism of their health benefits, life circumstances produced from seafood derived omega-3 (n-3) polyunsaturated fatty acids (PUFAs); EPA and docosahexaenoic acid (DHA), have been suggested. From ensuing various studies, as the therapeutic action of n-3 PUFAs not only the lowering of the triglyceride levels but also reducing the incidence of cardiovascular events were reported [2] [3]. The incidence of subclinical ischemic stroke in elderly patients who consume high levels of fish in their diet is lower than the incidence in those who do not [4] [5]. In addition, a low serum EPA level and a low EPA to AA ratio have been associated with unstableness of coronary artery disease [6]. EPA supplementation was found to be effective for the secondary prevention of coronary artery disease and in reducing the risk of recurrent stroke [6] [7]. Therefore, the PUFA balance might serve as an important diagnostic parameter for evaluating the extent of arteriosclerosis associated with coronary artery and cerebrovascular diseases [6] [7]. However, in therapeutic trials using n-3 supplements, the outcomes for the efficacy were varied and these results may be related to the quality of the supplements used. EPA drugs are prescribed as branded (EPADEL®: highly purified EPA ethyl ester) or generic products in Japan but no data exist regarding differences in the treatment outcomes between the products. Also, Jobu *et al.* conducted an accelerated test using the branded and several generic versions of a highly purified EPA and found that the decomposition products from autoxidation during storage produced odors, which may influence the drug adherence [8]. Therefore, we investigated the differences in EPA, DHA, AA and the EPA/AA ratio through blood sampling six months after daily administration of EPADEL® and a generic EPA product (released by a drug company) was initiated in patients with cardiovascular diseases.

2. Methods

2.1. Study Design

This study was carried out from January 2013 to June 2017 on 96 outpatients (64 men and 32 women, age range, 46 - 83 years) who had cardiovascular diseases and agreed to take n-3 supplements in the form of branded and generic products as well as to undergo blood sampling after taking the supplements.

We investigated the fasting serum levels of EPA, DHA and AA and the EPA/AA ratios through blood sampling performed six months after daily administration of 1800 mg of each product was initiated for these patients. The administration order for the PUFA products was not fixed and there was no washout period before administration of the second product.

Clinical data were obtained from all patients at the outpatient clinic with written informed consent. Patients underwent physical examination, blood

pressure measurement, chest radiography, electrocardiography, brain MRI, duplex ultrasonography of the carotid arteries, and laboratory examination including the measurement of the fasting plasma levels of fatty acids.

2.2. Study Patients

This study was approved by the review committee at Hokusetsu General Hospital. A total of 96 patients provided written informed consent.

Among these 96 patients, 60 had coronary artery disease, 80 exhibited hypertension with (n = 18) or without coronary artery disease, 78 had dyslipidemia with (n = 22) or without coronary artery disease, and 43 had diabetes with (n = 20) or without coronary artery disease.

The presence of hypertension was established if the patient had 1 of the following: systolic blood pressure > 160 mmHg or diastolic pressure > 90 mmHg, or if the patient used antihypertensive medications. The presence of dyslipidemia was established if the patient had a serum low-density lipoprotein level (LDL) ≥ 160 mg/dl or the patient received recent medication (mainly statin) for dyslipidemia. The presence of diabetes was established if the patient had a hemoglobin A1c value of ≥6.9% (NGSP) during the visit or if the patient received medication for hyperglycemia.

Sixty six of the patients maintained the same statin dose for dyslipidemia throughout the 12 months of treatment with branded and generic products, but the statin administration or the doses for the other 30 patients varied during this period. Therefore, we examined the PUFA and lipid levels separately among these sixty-six patients maintained the same statin dose.

2.3. Serum Examination of Lipids and Fatty Acids

The fasting serum levels for EPA, DHA, and AA were measured using gas chromatography at an external laboratory (SRL Inc., Tokyo, Japan). In this laboratory, the relationships between the sample dilution rate and the fatty acid concentration in gas chromatography are verified with good linearity. Also, they verify good simultaneous reproducibility and good sunlight reproducibility about their system, and their coefficient of variation are 1.77% - 5.60% and 6.99% - 8.16% in EPA, 1.02% - 3.83% and 5.55% - 7.94% in AA, and 1.18% - 5.71% and 4.53% - 6.25% in DHA, respectively. The effects of EPA products into dyslipidemia were examined with serum levels of LDL and triglyceride (TG).

2.4. Statistical Analysis

Two-tailed statistical analysis was performed with a 5% level of significance. The Wilcoxon 2-sample test was used to compare continuous variables. Statistical analyses were performed using JMP pro, version 9.0.2 (SAS Institute, Cary, NC, USA). Data are expressed as the mean ± standard deviation (SD).

3. Results

We examined the PUFAs level after treatment between the branded (EPADEL®)

and generic (a generic released by a drug company) products. The serum level of EPA in the patients evaluated was elevated with both the branded and generic products in comparison with the baseline data. The elevation with the branded product was greater than that with the generic product (Figure 1). The serum level of AA decreased with both the branded and generic products in comparison to the baseline data and the decrease with the branded product was greater than that with the generic product (Figure 2). The EPA/AA ratio was also elevated with both the branded and generic products in comparison to the baseline data and the increase with the branded product was greater than that with the generic product (Figure 3). In the evaluation of the 66 patients who took both products under the same statin dosage, the alteration of EPA levels was equivalent to the alteration among the overall 96 patients and there was no difference in the reduction in AA levels between the branded and generic products (Figure 4 and Figure 5). The EPA/AA ratio was also elevated with the branded and generic products in comparison to the baseline data and the alteration with the branded product was greater than that with the generic product among these 66 patients (Figure 6). The serum levels of DHA decreased with the branded and generic products in comparison to the baseline data but there was no difference in the reduction in DHA between the branded and generic products among the overall 96 patients and the 66 patients with the same statin treatment (Figure 7 and Figure 8).

The serum levels of LDL and TG decreased with both products and there was no distinction in the LDL and TG response with both EPA products among the 66 patients with the same statin treatment (Figure 9).

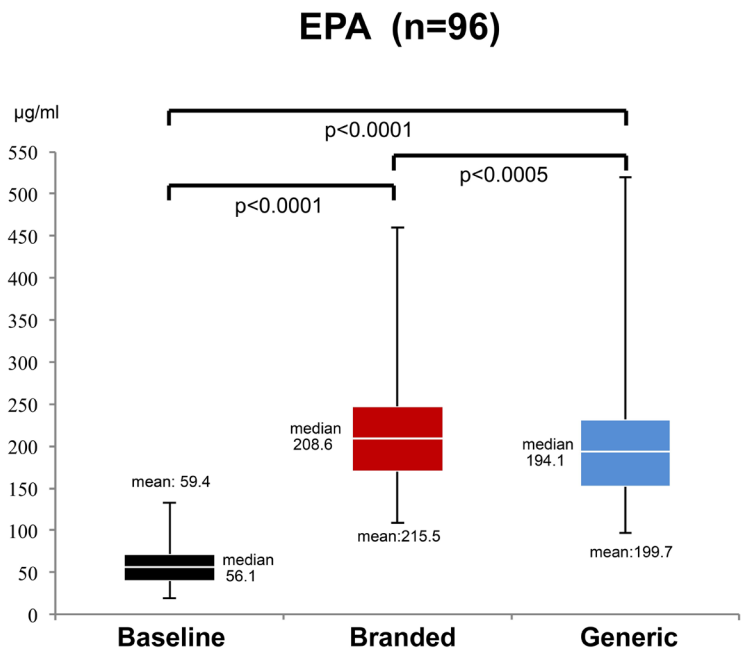

Figure 1. Box plots of serum levels of eicosapentaenoic acid (EPA) at the baseline and under administration of the branded and generic products. The serum EPA levels increased with the branded and generic products compared with the baseline data and the increase with the branded product was greater than that with the generic product.

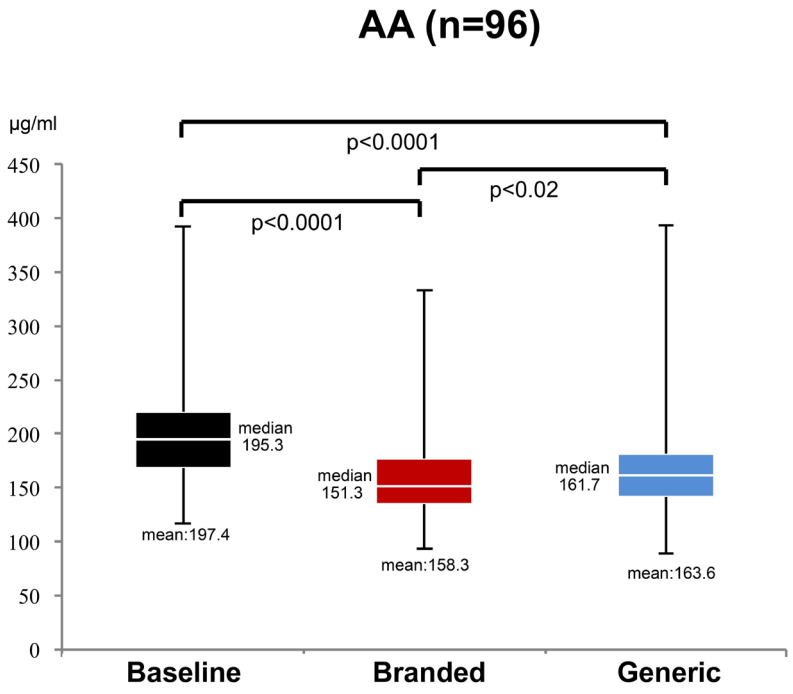

Figure 2. Box plots of serum levels of arachidonic acid (AA) at the baseline and under administration of the branded and generic products. The serum AA levels decreased with the branded and generic products compared with the baseline data and the decrease with the branded product was greater than that with the generic product.

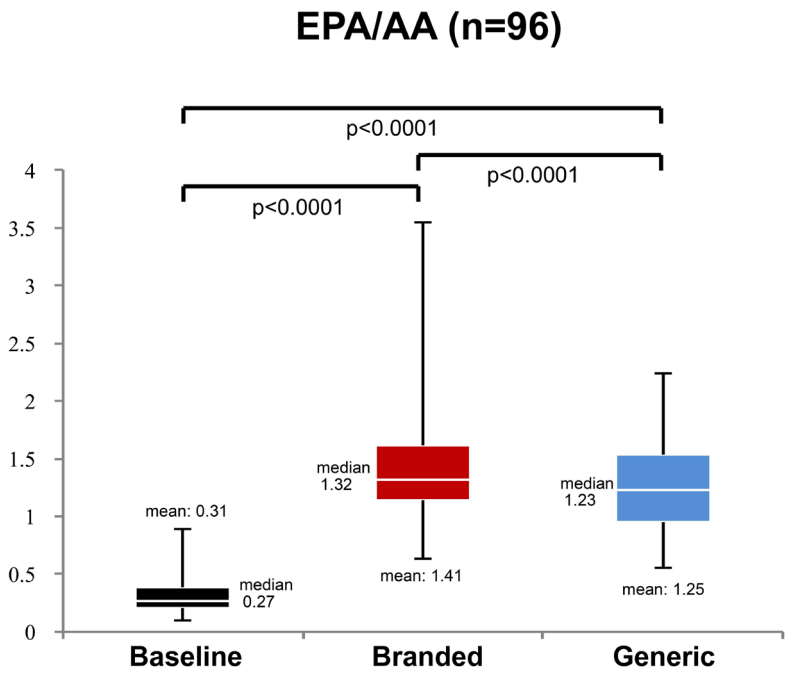

Figure 3. Box plots of serum EPA/AA ratio at the baseline and under administration of the branded and generic products. The EPA/AA ratio increased with the branded and generic products compared with the baseline data and the increase with the branded product was greater than that with the generic product.

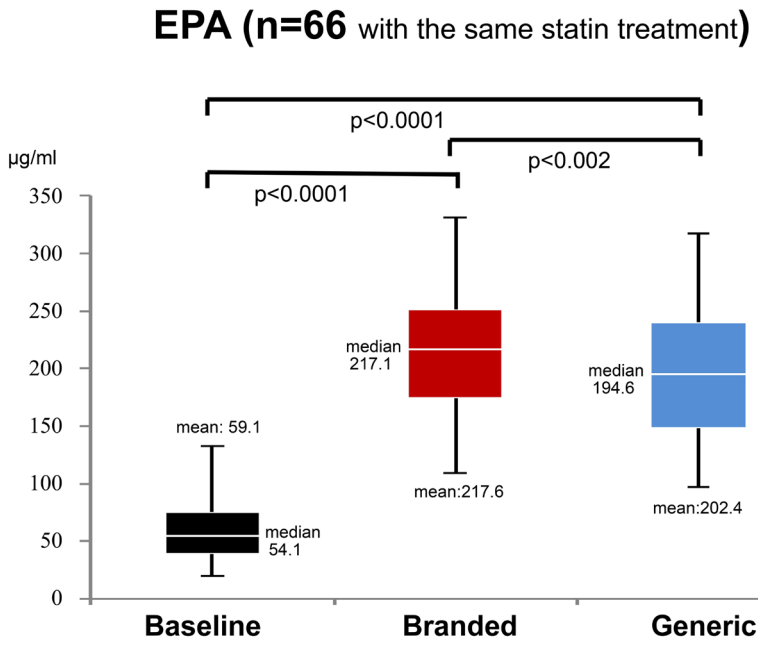

Figure 4. Box plots of serum EPA levels at the baseline and under administration of the branded and generic products among 66 patients who took both products with the same statin treatment. The serum EPA levels increased with the branded and generic products compared with the baseline data and the increase with the branded product was greater than that with the generic product.

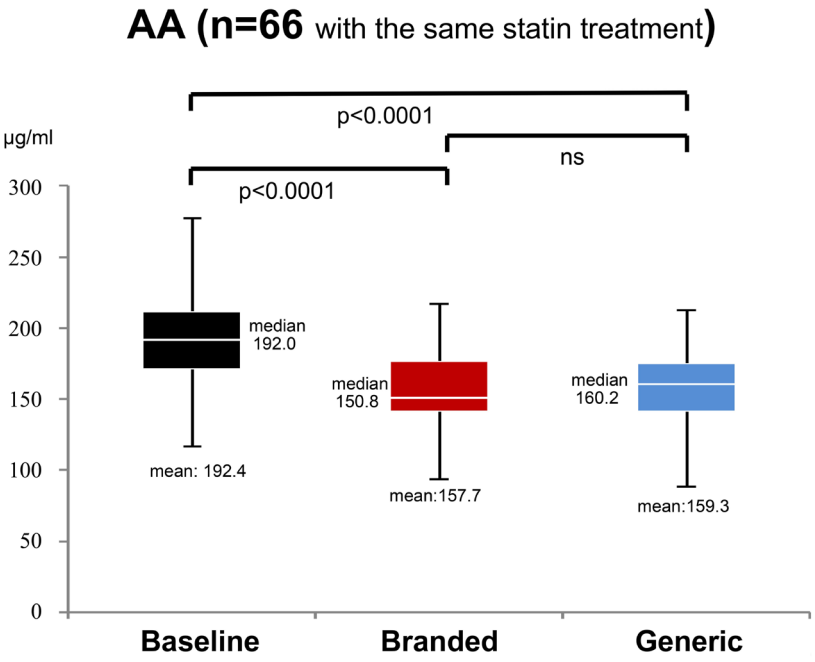

Figure 5. Box plots of serum AA levels at the baseline and under administration of the branded and generic products among 66 patients who took both products with the same statin treatment. The serum AA levels decreased with the branded and generic products compared with the baseline data and the degree of reduction was similar with the branded and generic product.

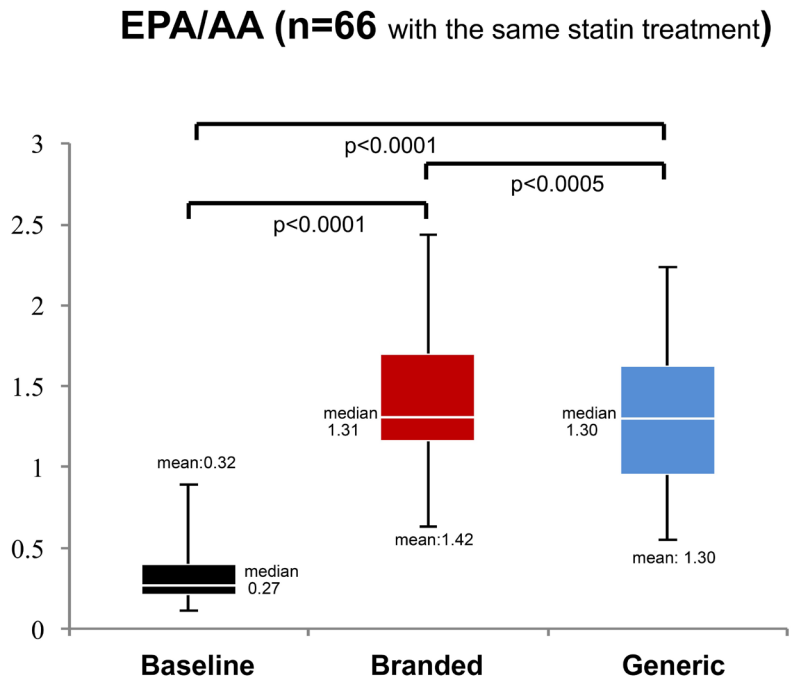

Figure 6. Box plots of serum EPA/AA ratio at the baseline and under administration of the branded and generic products among 66 patients who took both products with the same statin treatment. The EPA/AA ratio increased with the branded and generic products compared with the baseline data and the increase with the branded product was greater than that with the generic product.

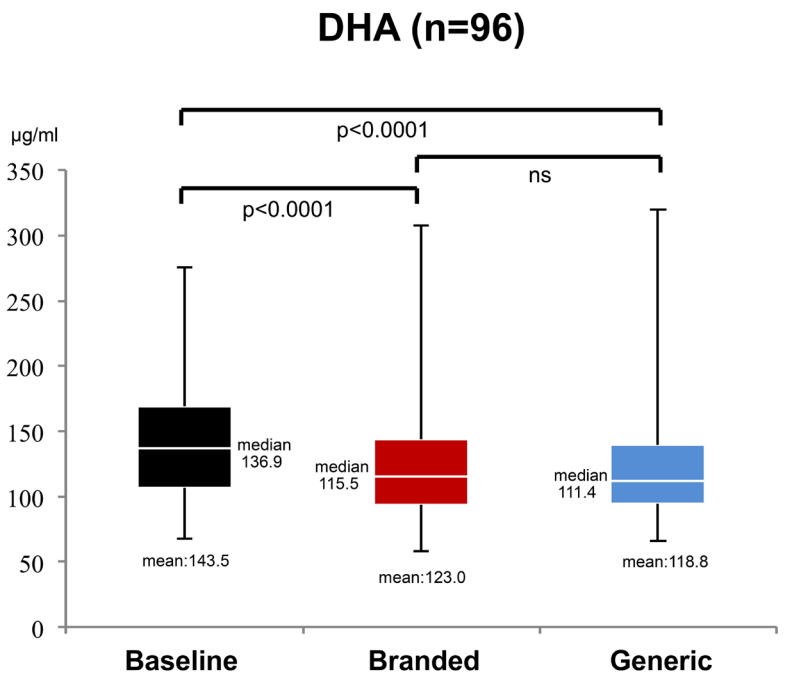

Figure 7. Box plots of serum levels of docosahexaenoic acid (DHA) at the baseline and under administration of the branded and generic products. The serum DHA levels decreased with the branded and generic products compared with the baseline data and the degree of reduction was similar with the branded and generic products.

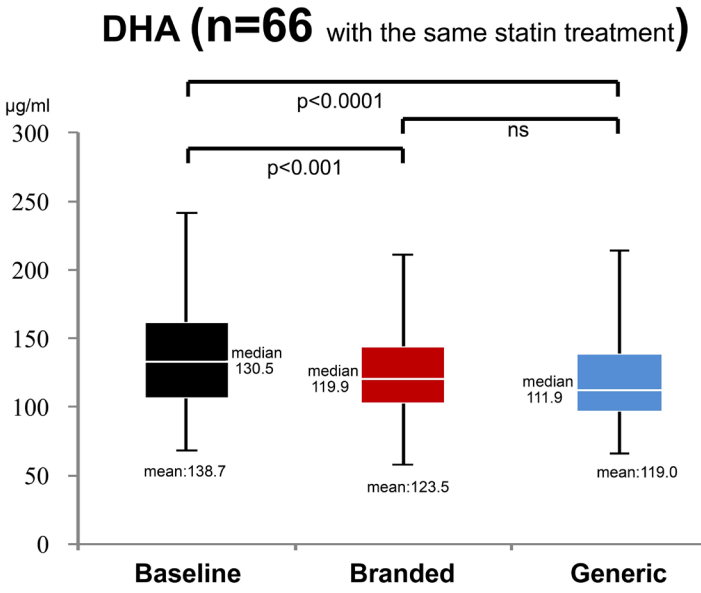

Figure 8. Box plots of serum levels of docosahexaenoic acid (DHA) at the baseline and under administration of the branded and generic products among 66 patients who took both products with the same statin treatment. The serum DHA levels decreased with the branded and generic products compared with the baseline data and the degree of reduction was similar with the branded and generic products.

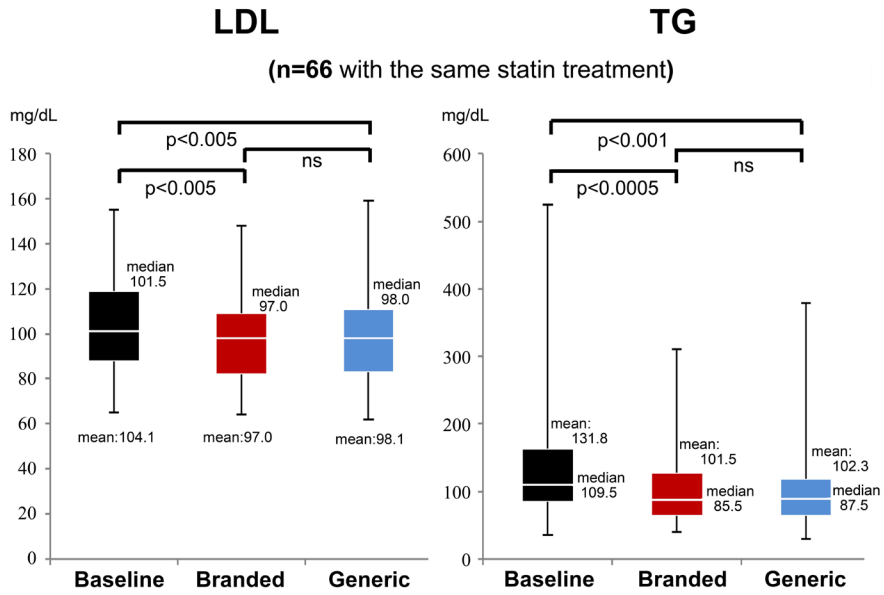

Figure 9. Box plots of serum levels of low-density lipoprotein (LDL) and triglyceride (TG) at the baseline and under administration of the branded and generic products among 66 patients who took both products with the same statin treatment. LDL and TG levels decreased with both products and there was no distinction in the LDL and TG response with both EPA products.

4. Discussion

The results of the present study indicated that the increase of EPA and the re-

duction of AA occurred as the therapeutic response to PUFA with EPA ethyl ester and the degree of improvement was superior with the branded product (EPADEL®), which is a being highly purified EPA ethyl ester, compared to the generic product.

Currently, n-3 acid ethyl esters containing both high purity ethyl esters of EPA and DHA, and icosapent ethyl being high purity prescription form of EPA ethyl ester are available as n-3 fatty acid prescription products along with their generic alternatives [2] [9]. The generics are widely available and low priced pharmaceutical products but the quality of the main component and the composition of the additives are not fully transparent. Comparisons of the biological equivalence and long-term storage of the branded and generic products are performed using parameters such as the maximum drug concentration, area under the blood concentration time curve and maximum drug concentration time.

4.1. Production Step of EPADEL®

As the first production step for EPADEL®, fish oil is extracted from sardines with a large EPA content as raw materials and environmental pollutants such as dioxin and free fatty acids are removed. EPA contained in the fish oil as a constituent of triglyceride is then hydrolyzed and becomes EPA-ethyl following ethyl esterification. The compounds also contain fatty acids unrelated to EPA, which are removed during the process with liquid chromatography and vacuum distillation. The result is a highly purified EPA-ethyl ester. As both the branded and generic products in this study met the official requirements for purity, conformed to the requirements in accelerated tests, and exhibited the same degree of TG and LDL reduction, it is unlikely that the amount and the content of EPA-ethyl in these two products are different. Based on the results from our evaluation, there may be some differences in the purification process for EPA ethyl ester between the two products. Currently, there is little information concerning the production process for generic products. These products may contain extra contaminants due to differences in the raw materials used or in the purification process. Jobu *et al.* conducted an accelerated test using the branded and several generic versions of a highly purified EPA and found that the decomposition products from autoxidation during storage produced odors, which may influence the drug adherence [8]. This problem was significantly suppressed by preservation with nitrogen gas replacement. Branded products are produced with highly technical procedures especially with regard to the packing, such as using nitrogen enclosures. This can lead to differences in drug adherence between the two types of products and reduce the effectiveness of the generic product.

Recent clinical investigations concerning to EPA products may have been performed with a mix of branded and generic products. This might explain the variable outcomes for the clinical implications of EPA products. Satoh-Asahara *et al.* reported that highly purified EPA treatment significantly increased the serum EPA/AA ratio and the ratio after the EPA treatment was significantly cor-

related with the interleukin-10 level in monocytes [10]. Expanding upon this mechanism, Calder *et al.* suggested that EPA can be metabolized to anti-inflammatory eicosanoids, partially replacing the AA in cell membranes and competitively inhibiting the production of AA and inflammatory eicosanoids, thereby exerting an anti-inflammatory effect [11]. Therefore, it might be meaningful that branded EPA products achieve a higher EPA/AA ratio.

4.2. Recent EPA Studies

There are several conflicting reports concerning to the effect of n-3 fatty acid on risk reduction in cardiovascular events. In the ASCEND study, n-3 acid ethyl esters (OMACOR® 1 g/day) containing both high purity ethyl esters of EPA (460 mg) and DHA (380 mg) were used for the treatment of patients with diabetes [12]. In the VITAL research, the same n-3 acid ethyl esters (1 g/day) containing both EPA (460 mg) and DHA (380 mg) were used for patients with cardiovascular disease and cancer [13]. No benefits were observed in these two studies from the use of n-3 fatty acid supplements. In contrast, the REDUCE-IT trial showed a significant risk reduction with highly purified EPA ethyl ester (VASCEPA® 4 g/day, containing 4000 mg EPA) [14] and the JERIS study also demonstrated significant risk reduction in secondary prevention with highly purified EPA ethyl ester (EPADEL® 1.8 g/day, containing 1800 mg EPA) [5]. Among these four studies, a clear conflict exists. The EPA content is clearly different and the quality of EPA may be related to the results as suggested in this study. In a recent study evaluating the effects of marine n-3 PUFAs on the risk of ischemic stroke, EPA was associated with lower risks for most types of ischemic stroke while inconsistent findings were observed for DHA [15]. There was a clear difference between EPA and DHA concerning the reduction in the risk of stroke from large artery atherosclerosis. This may be related to the fact that DHA increases LDL cholesterol [16]. However, as highly purified EPA ethyl ester reduces the DHA level, this speculation may not be valid.

4.3. Study Limitations

The limitations of this study are detailed below. The administration order for the PUFA products was not fixed. However, we did not apply a washout period before administration of the second product. Additionally, this study was performed at a single institution with a small sample size of ≤100 individuals because it is a real clinical investigation in an out-patient setting. Therefore, further evaluation is needed to determine whether the benefits from the branded product justify the higher cost compared to the generic drug.

5. Conclusion

The results of the present study indicated that the increase of EPA and the reduction of AA occurred as the therapeutic response to PUFA with EPA ethyl ester. The improvement was superior with the branded product (EPADEL®), which is a highly purified EPA ethyl ester, compared to the generic product.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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