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Research Article

Assessment of Biological Effectiveness of Omega-3-Fatty Supplements Using Holter ECG Analysis in Children

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Abstract

The main goal of our work was to check the biological effects of omega 3 fatty acid supplements using 24-hours heart rate variability as an objective parameter.

Methods: We analyzed 24-h heart rate variability in 136 children with a mean age of 10.5±5.0 years who received omega-3-fatty acid supplementation of cause elevated heart rates and reduced heart rate variability due to attention deficit disorder, heart disease, short stature, obesity and somatoform disorders. 116 children received different product from a retail store that are generally stabilized with Alpha-Tocopheryl Phosphate Mixture and 20 children received a product that certainly didn't include it.

Results: We found highly significant effects of omega 3 fatty acid supplements on heart rate both by day and at night as recently published. However, there is no heart rate lowering effect of the supplement without Alpha-Tocopheryl Phosphate Mixture. The heart rate lowering effect of omega-3-fatty acid supplements depends on heart rate at baseline, but not on the different indications and sex in childhood.

Conclusion: Bioavailability of omega-3-fatty acid supplements may explain the inconsistency of the clinical benefit of omega-3-fatty acid supplementation. We propose the manufacturer to proof the biological effectiveness of omega-3-fatty supplements using Holter ECG analysis in children.

Introduction

Omega-3-fatty supplementation has been proposed for many indications in children and adults and investigated in many prospective randomized trials. The most high-quality studies proof the impact of omega-3-fatty supplementation on cardiovascular risk in adults [1], but the results are still in debate. The current discussions focused on different doses and the bioavailability of omega-3-fatty supplements.

Within the last 20 years our research focused on autonomic dysfunction in childhood using 24-hours heart variability analysis. We routinely use omega-3-fatty acid supplementation in children with elevated heart rates and reduced heart rate variabilities after the observation of a significant decrease of elevated heart rates after three-month omega-3-fatty acid supplementation [2-4].

Swedish register data clearly show that an elevated resting heart rate in adolescence is an important cardiovascular risk factor for later all-cause mortality, most commonly due to the higher risk of heart failure [5].

Our primary intention to advice omega-3-fatty acids was to improve the enhanced cardiovascular risk in children with attention deficit disorder [6], obesity [7], arrhythmias [8,9] and short stature [10] but more and more we realize that nearly all children with elevated heart rates show clinical benefits after omega-3-fatty acid supplementation and the heart rates significantly decrease. However, human studies have started to sub-divide the subjects under study into omega-3-fatty acid responders and omega-3-fatty acid non responders, according individuals who are able to show or not the beneficial effects of omega-3-fatty acid supplementation.

In the current analysis we collect the data of 136 children who received omega-3-fatty acid supplementation to proof factors that predict the benefit of this treatment.

Materials and Methods

Patients

Based upon our hypotheses to treat autonomic dysfunction in childhood with omega-3-fatty acid supplementation, we analyzed 24-h HRV in 136 children with a mean age of 10.5±5.0 years, who were referred to the outpatient clinic in the Pediatrics Department of the Caritas Hospital, in Bad Mergentheim, Germany, between 2005 and 2019. For this analysis, we included two Holter ECG with a mean distance of 169 days of each patient before and after supplementation of omega-3-fatty acids. Some children received a pharmacotherapy e.g. with stimulants, growth hormone, antihypertensive drugs if indicated based upon the current guidelines. We routinely use omega-3-fatty acid supplementation in children with reduced heart rate variabilities and the following indications:

1. **Attention Deficit Disorder with/without Hyperactivity** (N=16). Pharmacotherapy: Methylphenidate=8, Amphetamine=1,

2. **Surgically treated Congenital Heart Disease** (N=10). Pharmacotherapy: Beta blocker = 3, Angiotensin-converting enzyme inhibitor =1, Digoxin=1,

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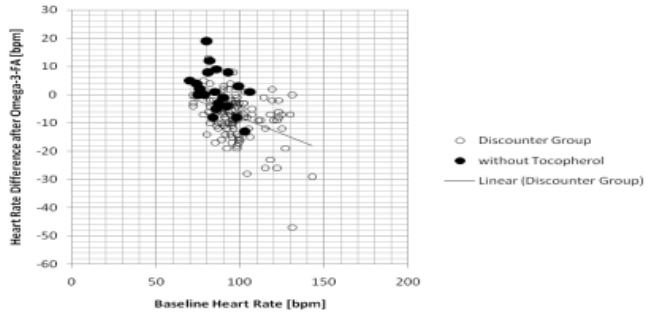

Figure 1: Effect of Omega-3-Fatty Acid Supplementation on the mean 24-hours Heart Rate.

3. **Arrhythmias** (N=18). Pharmacotherapy: Beta blocker=3,

4. **Short Stature** (N=31). Pharmacotherapy: Growth Hormone=13, Beta blocker=1,

5. **Obesity** (N=22). Pharmacotherapy: Beta blocker=1, Angiotensin-converting enzyme-inhibitor=1,

6. **Somatoforme Disorders** like chronic fatigue syndrome (N=19): No pharmacotherapy.

Omega-3-fatty acid supplementation

In those children with sinus tachycardia and significantly reduced 24-h HRV, we routinely offered the opportunity to supplement omega-3 fatty acids. If the supplementation was not covered by health insurance, patients purchased different products delivering 1-2 g fish oil per day from a retail store. The following dose recommendations were given: Children up to 8 years old should receive at least 400mg Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) as a suspension per day. Children who were able to swallow capsules should receive at least 800mg EPA and DHA per day.

We didn't know the specific product bought by the parents in the retail store in 116 children but we know that these products are generally stabilized with Alpha-Tocopheryl Phosphate Mixture as an antioxidant. 20 children received a product that certainly didn't include a Alpha-Tocopheryl Phosphate Mixture.

24-h ECG and analysis of heart rate variability

Fundamental to every HRV data analysis is a group of successive normal RR intervals in sinus rhythm over a period of 24 h. In HVR these are called NN intervals to distinguish them from the RR intervals in cardiac arrhythmia. Measurement and interpretation of HRV parameters in the current sample were standardized according to the Task Force Guidelines [11]. Cardiac autonomic functioning was measured by 24-h Holter 12-bit digital ECG (Reynolds Pathfinder II, Spacelabs, Germany; 1024 scans/sec). Day- and nighttime periods were defined according to patient protocols. All Holter recordings were reviewed by the same experienced cardiologists and were edited to validate the system's QRS labeling. Measures of HRV were calculated employing only NN intervals. QRS-complexes classified as noise were excluded from the data. A minimum of 23 h of analyzable data and minimum of 95% of analyzable NN intervals were required for data to be included. For time domain measures, mean NN interval, resulting heart rate, and HRV parameters outlined below were calculated.

For didactic reasons, in this study, we focused on the statistical analysis of the following four parameters:

Heart rate: The easiest, but very important, HRV parameter is the average sinus rhythm heart rate, since all other parameters are significantly affected by the heart rate.

Standard Deviation of all Normal NN intervals in a time frame (SDNN): This global HRV parameter represents the overall variability of the autonomic nervous system.

Square root of the arithmetic mean of the squared deviation of successive normal NN intervals in a time frame (rMSSD): This parameter is mainly influenced by the parasympathetic nervous system.

For frequency domain measures, beat-to-beat fluctuations were transformed to the frequency domain using Fast Fourier Transformation. Spectral power was determined over three frequency regions of interest: very low frequency (VLF, <0.04 Hz), low frequency (LF, 0.04-0.15 Hz), and high frequency (HF, 0.1-0.4 Hz) with derived HF/LF ratios.

Blood pressure

For blood pressure measurements we used oscillometric (automated) blood pressure measurement devices (Bionics Sentry™, South Korea), which have rapidly replaced sphygmomanometers in clinical practice. These devices are more ecologically friendly, easier to use, and eliminate potential sources of bias. Records are digitally displayed as systolic- and diastolic blood pressure, and heart rate. The internal bladder (inflatable area) of the cuff must encircle 90-100% of the circumference of the upper arm.

Statistical analysis

Data were expressed as mean±standard deviation. As most variables exhibited a normal distribution, between-group differences were assessed using parametric statistics. We used a paired student t-test to analyze the effect of omega-3-fatty acid supplementation on HRV. The current the group was subdivided in the so-called discounter group and a second group who received omega-3 fatty acids without an Alpha-Tocopheryl Phosphate Mixture (Table1). Significant group differences were anticipated if the p-value was <0.05. All analyses were performed using IBM SPSS Statistics software, Version 25 (IBM Corp. IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY, USA).

Based upon our recent published studies we know that omega-3-fatty acids significantly reduce the mean 24-hours heart rate [6-8, 10]. For further analysis we proof the effect of omega-3-fatty acids on the heart rate (Heart rate after supplementation-Heart rate at baseline) in a subgroup analysis using One-way Analysis of variance (Table 2). We further stratified the so called discounter group into the following subgroups:

1. Based upon the Baseline Heart Rate [bpm]: <80bpm; 80-89bpm; >90bpm,

2. Indication: Attention Deficit Disorder, Heart Disease, Arrhythmias, Short Stature, Obesity, Somatoform Disorder,

3. Age [Years]: <6 years; 6-10 years; >10 years,

4. Sex: female/male.

Table 1: 24-hours heart rate variability before and after Omega-3-fatty supplementation.

	Discounter Group (N=116)					Tocopherolfree Group (N=20)				
	Baseline		Omega-3-Fatty Acids			Baseline		Omega-3-Fatty Acids		
	Mean	SD	Mean	SD	P-value	Mean	SD	Mean	SD	P-value
Sys BP [mmHG]	116,5	15,0	116,3	13,7	0,87	122,6	12,3	125,4	13,6	0,278
Diast. BP [mmHG]	62,0	13,7	61,1	12,2	0,643	66,3	11,6	66,8	10,7	0,846
Heart Rate [bpm]	98,1	14,1	90,5	13,2	0	86,3	9,9	87,8	9,7	0,383
Heart Rate Day [bpm]	106,7	16,3	100,5	18,3	0,001	95,4	10,9	95,5	12,0	0,976
Heart Rate Night [bpm]	86,6	16,1	78,7	13,4	0	75,6	10,8	76,1	11,0	0,744
SDNN [ms]	112,7	38,8	131,0	37,6	0	140,0	39,8	142,0	50,5	0,776
RMSSD [ms]	27,5	13,0	35,2	15,1	0	38,1	13,8	35,6	13,4	0,245
Total Power [ms²]	3192	2643	4281	2859	0	4311	2141	3774	2503	0,146
VLF Power [ms²]	1714	1710	2267	1612	0	2508	1341	2255	1663	0,23
LF Power [ms²]	792	585	1036	620	0	1115	615	935	504	0,1
HF Power [ms²]	496	607	752	945	0,003	615	399	516	407	0,228
HF/LF Ratio	0,71	0,56	0,71	0,56	0,329	0,53	0,21	0,54	0,30	0,944

BP: Blood Pressure; SDNN: Standard Deviation of all NN intervals; RMSSD: The Square Root of the Mean of the Sum of the Squares of Differences between Adjacent NN intervals; TP: Total Power; VLF: Very low Frequency power; LF: Low Frequency power; HF: High Frequency power; HF/LF: Ratio HF to LF.

Results

We prescribed omega-3-fatty acid supplementation and 116 patients bought products in the retail store, as shown in Table 1. We separately analyze 20 children who received a product that certainly didn't include an Alpha-Tocopheryl Phosphate Mixture. In first group of 116, we found highly significant effects on heart rate both by day and at night as recently published [6-8,10] The significant heart rate decrease of 7.6bpm over 24 h, 6.2bpm at daytime, and 7.9bpm at night, is related to a significantly higher HRV. Significantly higher RMSSD, and high-frequency power values indicate a higher vagus activity after omega-3-fatty acid supplementation. However, as shown in all our published studies about omega-3-fatty acid supplementation, the HRV improves across the whole power spectrum of the Fast Fourier Analysis with nearly no effect on the HF/LF ratio. This could be an evidence of a specific effect of omega-3-fatty acid supplementation in children with autonomic dysfunction that not only depends on the autonomic system but also upon its effect on specific ion channels of the sinoatrial node. The sinoatrial node pacemaker cells are the end effector of circadian heart rate variation that not only depend on the dual regulation by the vagus nerve and sympathetic nervous system [12].

The 20 children who received a product that certainly didn't include an Alpha-Tocopheryl Phosphate Mixture showed no significant effects on 24-hours HRV. At baseline this group had lower mean heart rates and higher heart rate variabilities (Table 1).

If we stratified the so called discounter group based upon the heart at baseline, we found a statistically significant effect of the baseline heart rate on the heart rate decrease after omega-3-fatty acid supplementation (Table 2) that seems to be most effective in children with heart rates >100bpm (-11bpm; p=0.003). We found no significant of the indication group, age or sex on the heart rate decrease due to omega-3-fatty acid supplementation.

Discussion

The main goal of our work was to check the biological effects of omega 3 fatty acid supplements using 24-hours HRV as an objective parameter. As recently published [6-8,10], omega-3-fatty acid supplementation significantly decreases heart rate in children with autonomic dysfunction. Moreover, the significant heart rate decrease of 7.6bpm over 24 h in children is much higher than the heart rate lowering effect of omega-3-fatty acid supplementation

Table 2: Heart Rate Difference after Omega-3-Fatty Acid Supplementation.

Stratifikation			Heart Rate Difference: Omega-3-FA-Baseline		
		N	Mean	SD	P-value
Baseline Heart Rate [bpm]	<90	28	-4,1	7,2	
	90-99	52	-7,0	6,4	
	>100	36	-11,0	10,2	
	All	116	-7,6	8,3	0,003
Indication	Attention Deficit Disorder	16	-7,8	7,7	
	Heart Disease	10	-6	5,3	
	Arrhythmias	18	-6,3	7,3	
	Short Stature	31	-8,3	10,4	
	Obesity	22	-8,2	7,7	
	Somatoform Disorder	19	-7,6	8,3	
	All	116	-7,6	8,3	0,953
Age [Years]	<6	27	-9,8	10,4	
	10-Jun	30	-7,9	7,1	
	>10	59	-6,3	7,6	
	All	116	-7,6	8,3	0,188
Sex	Girl	52	-6,8	7,8	
	Boy	64	-8,2	8,6	0,39

in adults (-2.23bpm; 95% CI:-3.07,-1.40bpm) as shown in a recent meta-analysis [4]. We decide to use this heart rate lowering effect as a target for therapy control foromega-3-fatty acid supplementation in different indications and products.

However, our research is completely altruistic and we have no opportunity to supplement the children with a uniformly defined composition and dose, if the supplementation was not covered by health insurance and the parents of 119 children had to purchase different products delivering from a retail store. We had the opportunity to proof the effect of Alpha-Tocopheryl Phosphate Mixture as an antioxidant after one manufacturer provided us with his preparation without Alpha-Tocopheryl Phosphate Mixturefor 20 children free of charge.

To our surprise this group of 20 children who was supplemented with an omega-3-fatty acid supplement without an Alpha-Tocopheryl Phosphate mixture is the first who didn't show the heart rate lowering effect (Table 1). As shown in the figure, only 2 of these 20 children show a heart rate lowering effects below the regression line. A recent study in rats demonstrated that co-administering omega-3 fatty acids with an Alpha-Tocopheryl Phosphate Mixture significantly increases the bioavailability of docosahexaenoic acid in the plasma [13]. It may be possible that the contradicting results in the huge number of clinical studies may explained by the different bioavailability of the products. This must be proofed by plasma measurements that is standard of care in pharmacotherapy but was obviously neglected for nutritional supplements.

Moreover, we are able to sub-divide our study group in responders and non-responders of omega-3-fatty acid supplementation based upon the heart rate lowering effect. This heart rate lowering effect of omega-3-fatty acid supplementation depends most of all on the baseline heart rate (Table 2, Figure 1). The baseline heart rate depends on age in healthy children. However, it is less the age but the elevated heart rate due to autonomic dysfunction that predicts the biological effect of omega-3-fatty supplementation on heart rate in our analysis. It has been shown that heart rate is elevated in children with attention deficit disorder [14], arrhythmias [8], short stature [15], and obesity [16]. We found a comparable heart rate lowering effect in all these indications. Sex seems not to predict the effect of omega-3-fatty supplementation if we found comparable effects in girls and boys.

We are aware of the methodological limitations of this analysis that depends on the altruistic nature of our research without any financial support. However, we don't understand that basic pharmacokinetic measurements are neglected in most of the more than 5000 clinical trials about omega-3-fatty acid supplementation listed in PubMed.gov. We propose the manufacturer to proof the biological effectiveness of their omega-3-fatty products using Holter ECG analysis in children.

References

1. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. The Cochrane database of systematic reviews. 2020; 3: Cd003177.
2. La Rovere MT, Christensen JH. The autonomic nervous system and cardiovascular disease: role of n-3 PUFAs. Vascul Pharmacol. 2015; 71: 1-10.
3. Drewery ML, Spedale SB, Lammi-Keefe CJ. Modulation of heart rate and heart rate variability by n-3 long chain polyunsaturated fatty acids: Speculation on mechanism(s). Medical hypotheses. 2017; 107: 29-34.
4. Hidayat K, Yang J, Zhang Z, Chen GC, Qin LQ, Eggersdorfer M, et al. Effect of omega-3 long-chain polyunsaturated fatty acid supplementation on heart rate: a meta-analysis of randomized controlled trials. European journal of clinical nutrition. 2018; 72: 805-817.
5. Lindgren M, Robertson J, Adiels M, Schaufelberger M, Aberg M, Toren K, et al. Resting heart rate in late adolescence and long term risk of cardiovascular disease in Swedish men. International journal of cardiology. 2018; 259: 109-115.
6. Buchhorn R, Koenig J, Jarczok MN, Eichholz H, Willaschek C, Thayer JF, et al. A case series on the potential effect of omega-3-fatty acid supplementation on 24-h heart rate variability and its circadian variation in children with attention deficit (hyperactivity) disorder. Attention deficit and hyperactivity disorders. 2018; 10: 135-139.
7. Baumann C, Rakowski U, Buchhorn R. Omega-3 Fatty Acid Supplementation Improves Heart Rate Variability in Obese Children. International journal of pediatrics. 2018; 2018: 8789604.
8. Buchhorn R, Baumann C, Willaschek C. Alleviation of arrhythmia burden in children with frequent idiopathic premature ventricular contractions by omega-3-fatty acid supplementation. International journal of cardiology. 2019; 291: 52-56.
9. Buchhorn R, Willaschek C. Resolution of a therapy-resistant focal atrial tachycardia after omega-3 fatty acid supplementation. Cardiology in the young. 2019; 29: 989-992.
10. Buchhorn R, Willaschek C, Norozi K. Improving Heart Rate Variability in Children with Short Stature by Supplementing Omega-3-Fatty Acids. J Food Nutr Popul Health. 2017; 1: 16.
11. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996; 93: 1043-1065.
12. Yaniv Y, Lakatta EG. The end effector of circadian heart rate variation: the sinoatrial node pacemaker cell. BMB reports. 2015; 48: 677-684.
13. Libinaki R, Gavin PD. Changes in Bioavailability of Omega-3 (DHA) through Alpha-Tocopheryl Phosphate Mixture (TPM) after Oral Administration in Rats. Nutrients. 2017; 9.
14. Buchhorn R, Conzelmann A, Willaschek C, Stork D, Taurines R, Renner TJ. Heart rate variability and methylphenidate in children with ADHD. Atten Defic Hyperact Disord. 2012; 4: 85-91.
15. Buchhorn R, Meint S, Willaschek C. The Impact of Early Life Stress on Growth and Cardiovascular Risk: A Possible Example for Autonomic Imprinting? PloS one. 2016; 11: e0166447.
16. Buchhorn R HF, Meint S, Willaschek C. The Impact of Nutrition on the Autonomic Nervous System. Int J Food Nutr Sci. 2016; 3: 1-16.