Original Article

Efficacy of Omega-3 Fatty Acids in the Treatment of Carpal Tunnel Syndrome: A Randomized Double-Blind Controlled Trial

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Background: Omega-3 fatty acids have anti-inflammatory and neuroprotective effects. However, there is no clinical trial to evaluate the efficacy of omega-3 fatty acids in the treatment of carpal tunnel syndrome (CTS).

Objective: To study the efficacy of omega-3 fatty acids (1,200 and 3,000 mg) administration compared with conventional treatment for three months in patients with mild to moderate CTS.

Materials and Methods: A randomized double-blind controlled trial was conducted in Thammasat University Hospital, Thailand between March 2017 and December 2018. Patients with mild to moderate CTS were randomly assigned into three treatments: 1) oral fish oil, EPA/DHA 1,200 mg per day, 2) fish oil 3,000 mg per day, and 3) placebo. All patients received vitamin B as a conventional treatment. Patients and research assistant who gave a concealed container were blinded to the group assignment. The primary outcomes were numbness and pain scores, which were measured monthly in numeric rating scale (NRS 0 to 10) for three months. Linear mixed models were used to analyze correlated data.

Results: Twenty-eight patients with 42 CTS hands were analyzed: 1) fish oil 1,200 mg group (n=9, hand=13), 2) fish oil 3,000 mg group (n=10, hand=16), and 3) control group (n=9, hand=13). A duration of symptoms was the only different variable between the three groups in univariable analysis. After adjustment for duration of symptoms, the mean differences of numbness and pain score were monthly reduced 0.6 points (95% CI –1.2 to –0.1, p=0.017) and 0.8 points (95% CI –1.3 to –0.2, p=0.005), respectively, in the fish oil 3,000 mg group compared with the control group. However, there was no statistically significant difference in any score between the fish oil 1,200 mg group and the control group. Heartburn and abdominal discomfort were found similarly in the three groups. There were no serious side effects in the present study.

Conclusion: Omega-3 fatty acids (EPA/DHA 3,000 mg per day) reduce numbness and pain with statistical significant difference in treatment of mild to moderate CTS. However, clinical significance was still in doubt and need further research to explore.

Keywords: Omega-3, EPA/DHA, Fish oil, Carpal tunnel syndrome

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Carpal tunnel syndrome (CTS) is the most common neuropathy of the upper extremity caused by compression of the median nerve at the level of the carpal tunnel[1]. In Thailand, the prevalence of computer work-related CTS was 33.8%[2]. CTS was common among people in 45 to 60 years old and women[3]. Symptoms are usually bilateral[4]. Patients commonly have nocturnal symptoms, muscle atrophy, pain, and paresthesia in median dermatome. They need to shake their hands to relieve these symptoms, an action known as the "flick sign"[3,5,6]. An electrodiagnostic study is essential to diagnose CTS and evaluate the severity of the median nerve injury[3].

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The management of CTS is divided into conservative and surgical treatment. Mild to moderate CTS is initially conservatively treated. The effective treatments of CTS are a night wrist splint and local steroid injection, but vitamin B is ineffective[7,8]. However, patients with mild to moderate CTS receive vitamin B as an initial conservative treatment. Theoretically, vitamin B plays a role in myelination and the inflammatory response. Vitamin B improved the CTS symptoms in a retrospective review but did not alleviate them in a clinical trial[9,10]. In addition, patients tend to avoid a local steroid injection due to fear of nerve or tendon rupture. Surgical decompression is frequently used in a patient with severe or persistent symptoms. More than half of patients that have been conservatively treated still proceed to a surgical decompression[11,12].

Omega-3 fatty acids are polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)[13,14]. They can be found in seafood and fish oil supplements. Omega-3 fatty acids are widely used as a supplement for anti-inflammation, pain reduction, and neuroprotective effects. Moreover, omega-3 fatty acids that have a high level of DHA can help to stimulate nerve remyelination and recovery[15,16]. Previous studies used omega-3 fatty acids in the treatment of non-surgical neck or back pain[17], rheumatoid arthritis[18,19], cervical radiculopathy[20], and multiple sclerosis[15]. However, there has not been a clinical trial that used omega-3 fatty acids in the treatment of CTS.

The present study aimed to evaluate the change of numbness score, pain score, Thai-version Boston carpal tunnel questionnaire (BQ) score, and electrodiagnostic severity in treatment of CTS after omega-3 fatty acids administration compared with conventional treatment for three months.

Materials and Methods

A randomized double-blind controlled trial was approved by the Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine) on May 12, 2016 and registered in the Thai Clinical Trials Registry (TCTR No.20160809001). Patients with CTS by clinical diagnostic criteria at Physical Medicine and Rehabilitation clinic, Thammasat University Hospital were recruited into the present study between March 2017 and December 2018. Clinical diagnostic criteria were paresthesia in median nerve distribution, nocturnal paresthesia, pain at the wrist that may radiate to the forearm, arm, and shoulder when provoked by wrist flexion or extension and can be relieved with the "flick sign", weakness of thumb abduction and opposition, hypotrophy or atrophy of thenar eminence, and positive results of Tinel's sign or Modified Phalen's tests. Inclusion criteria were age between 18 and 60 years and mild to moderate degree of CTS by electrodiagnostic criteria. Exclusion criteria were carpal tunnel release or steroid injection, omega-3 fatty acid supplementation within the past three months, evidence of underlying disorders such as bleeding tendency, diabetes mellitus, and cervical radiculopathy, use of warfarin, clopidogrel, or aspirin, allergy to fish oil and seafood, and pregnancy.

The patients were selected based on the inclusion and exclusion criteria. Patients were randomized into three groups (1:1:1 ratio) by blocked randomization via computer-generated numbers. The concealed envelopes with serial numbers and group assignments were prepared.

Patients were informed about the present study. They signed an information consent prior to the beginning of the study. A researcher opened a concealed envelope containing serial numbers and group assignments. Patients were assigned into three groups by a researcher. The experimental group 1 (fish oil 1,200 mg group) received four capsules of fish oil (EPA:DHA ratio as 1:5, 300 mg/capsule) and six capsules of placebo (methyl cellulose) (10 capsules daily). The experimental group 2 (fish oil 3,000 mg group) received 10 capsules of fish oil daily. The control group received 10 capsules of placebo daily. The placebo capsules were similar in color and appearance to the fish oil capsules. The 10 capsules of fish oil or placebo were administered three times per day after a meal for over three months. All three groups also received one tablet of vitamin B complex, taken orally three times per day. The rationale for the dose of fish oil 1,200 mg and 3,000 mg followed a previous study to reduce pain in non-surgical neck or back pain and reduce global symptoms scores in CTS[17,20]. A research assistant gave a concealed package to the patients followed by a serial number. The patients and the research assistant were blinded to the group assignment. The patients were informed to contact the researchers in 1, 2, and 3 months. Anyone with serious fish oil side effects or in need of a steroid injection or surgical decompression would be removed from the present study.

Primary outcomes were measured with the numeric rating scale (NRS) of numbness and pain. The NRS ranges from 0 (no symptom) to 10 (most severe). The outcomes were assessed at baseline, 1, 2, and 3 months by a patient self-assessment. Patients

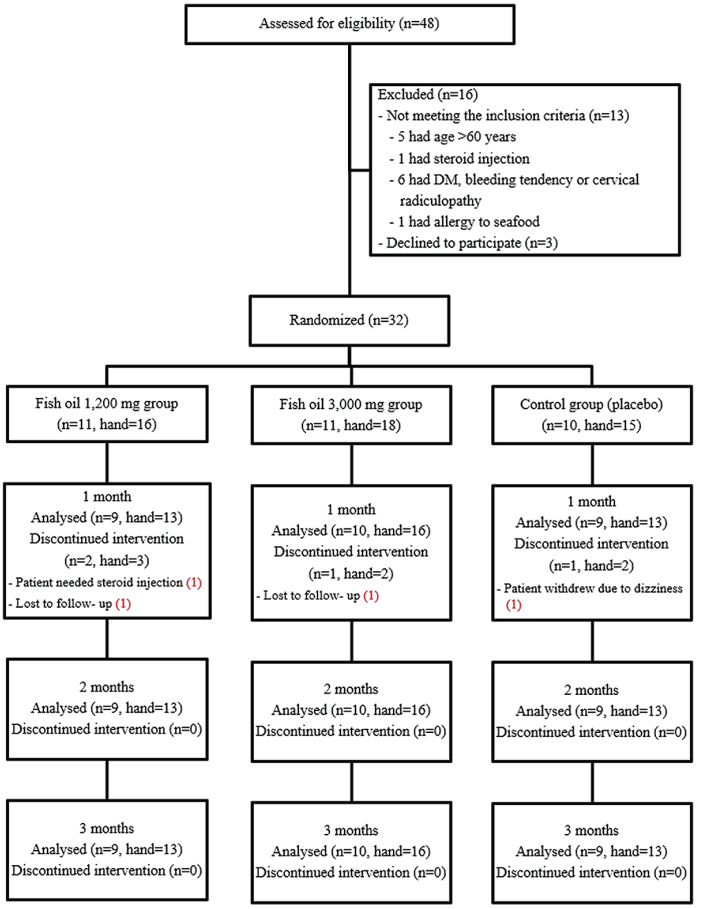

Figure 1. Participant flow in the study.

with bilateral CTS were separately evaluated with the NRS in each symptomatic hand.

Secondary outcomes were measured with the Thai-version BQ and the electrodiagnostic study. The Thai-version BQ consisted of 11 items of symptom severity scores (SSS) and eight items of functional severity scores (FSS). The internal consistency for the Thai-version BQ was 0.86 and 0.84 in the SSS and FSS, respectively. The items of each scale were given a score from 1 (mildest) to 5 (most severe). The SSS scale was sensitive to clinical change[21]. The outcomes of the Thai-version BQ were assessed on a baseline, 1, 2, and 3 months by a patient self-assessment. Patients with bilateral CTS were evaluated with the BQ in the most symptomatic hand.

The electrodiagnostic study evaluated median sensory and motor nerve conduction study (NCS) by a researcher who was qualified by the Rehabilitation Medicine Board. The severity of CTS was divided into three degrees (mild, moderate, and severe) by the American Association of Electrodiagnostic Medicine (AAEM) criteria[22]. The NCS outcomes were recorded at baseline and followed up in the third month. Patients with bilateral CTS were separately evaluated with the NCS in each symptomatic hand.

Statistical analysis

The estimated sample size was calculated through the three-sample comparison of mean. The preliminary data of mean NRS difference for numbness and pain were used to calculate the sample size in each group (alpha 0.05 (two-sided), power 0.8, mean difference ± standard deviation in population 1: numbness –2.6±1.2, pain –1.8±1.5; in population 2: numbness –3.7±1.2, pain –2.7±1.6; in population 3: numbness –1.7±1.0, pain 0.9±1.2). The estimated required number of hands in each group was 11.

The analysis was performed according to per-protocol principles. Categorical data were presented as frequency and percentages. Continuous data were presented as mean, median, standard deviation, and interquartile range, depending on the nature

Table 1. Demographic and baseline characteristics of the patients

Parameters	Fish oil 1,200 mg group n=9, hand=13 n (%)	Fish oil 3,000 mg group n=10, hand=16 n (%)	Control group n=9, hand=13 n (%)	p-value
Age (years)				0.581
Mean±SD	48.6±6.3	44.7±10.0	47.1±7.2	
Median (P_{25}, P_{75})	47 (45, 54)	46 (40, 50)	49 (42, 50)	
Sex				0.190
Male	0 (0)	0 (0)	2 (22)	
Female	9 (100)	10 (100)	7 (78)	
BMI (kg/m^2)				0.298
<22.9	1 (11)	4 (40)	1 (11)	
≥23	8 (89)	6 (60)	8 (89)	
Occupation				0.115
Office	4 (44)	7 (70)	4 (44)	
Housekeeper	4 (44)	1 (10)	1 (12)	
Vender	0 (0)	2 (20)	4 (44)	
Farmer	1 (12)	0 (0)	0 (0)	
Symptomatic hand				0.476
Right	3 (33)	4 (40)	5 (56)	
Left	2 (22)	0 (0)	0 (0)	
Both sides	4 (45)	6 (60)	4 (44)	
Duration of symptoms (months)				0.042*
Mean±SD	18.8±38.3	8.4±7.1	25.4±17.3	
Median (P_{25}, P_{75})	6 (2, 12)	8 (2, 12)	24 (12, 36)	
Baseline NRS for numbness; mean±SD	6.4±2.8	5.8±2.6	5.5±2.3	0.810
Baseline NRS for pain; mean±SD	4.4±3.3	4.1±3.1	3.2±3.0	0.596
Baseline SSS; mean±SD	29.3±7.8	28.2±5.9	29.6±8.9	0.916
Baseline FSS; mean±SD	17.9±6.9	13.9±4.6	17.8±8.0	0.336

BMI=body mass index; NRS=numeric rating scale; SSS=symptom severity score; FSS=functional severity score; SD=standard deviation

* Statistical significance, p<0.05

of the data. To compare demographic and baseline characteristic data among groups, the authors used Fisher's exact test for categorical data, and the ANOVA and Kruskal-Wallis tests for continuous data. The authors took into account the correlation between observed data, such as symptomatic hands in the same patients and repeated measurement of numbness or pain in each hand monthly, by using a linear mixed-effect model for analysis of treatment efficacy within and among groups. The authors also adjusted the duration of symptoms among group analyses because this factor showed difference in univariable analyses. Among the groups' comparison of electrodiagnostic CTS severity and side effects event were conducted using Fisher's exact test. Statistical significance was accepted at p-value less than 0.05. The data were analyzed using Stata, version 12.1 (StataCorp LP, College Station, TX, USA).

Results

The present study had thirty-two patients randomly divided into three groups. Eleven patients (16 symptomatic hands) were assigned to the fish oil 1,200 mg group, 11 patients (18 symptomatic hands) to the fish oil 3,000 mg group, and 10 patients (15 symptomatic hands) to the control group. One patient needed steroid injections. Two patients were lost to follow-up. One patient withdrew from the study due to dizziness (see Figure 1). Twenty-eight patients (42 symptomatic hands) were analyzed in original assigned groups. Nine patients (13 symptomatic hands) were analyzed in the fish oil 1,200 mg group,

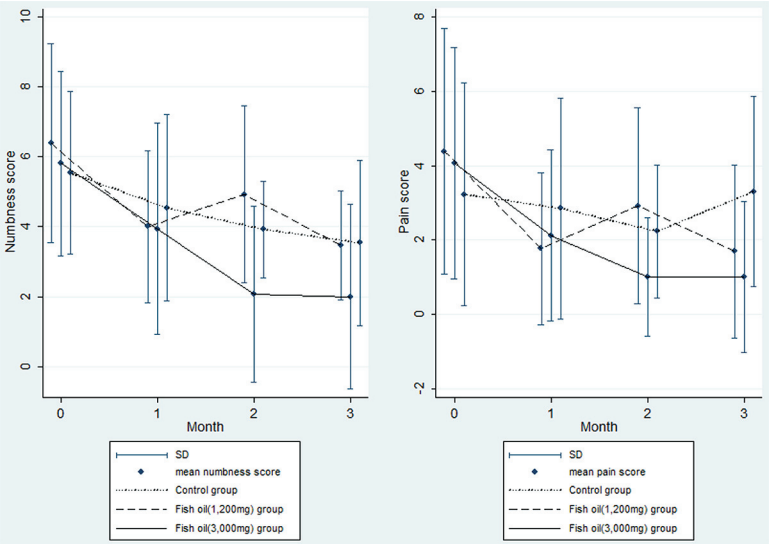

Figure 2. Numeric rating scale for numbness and pain.

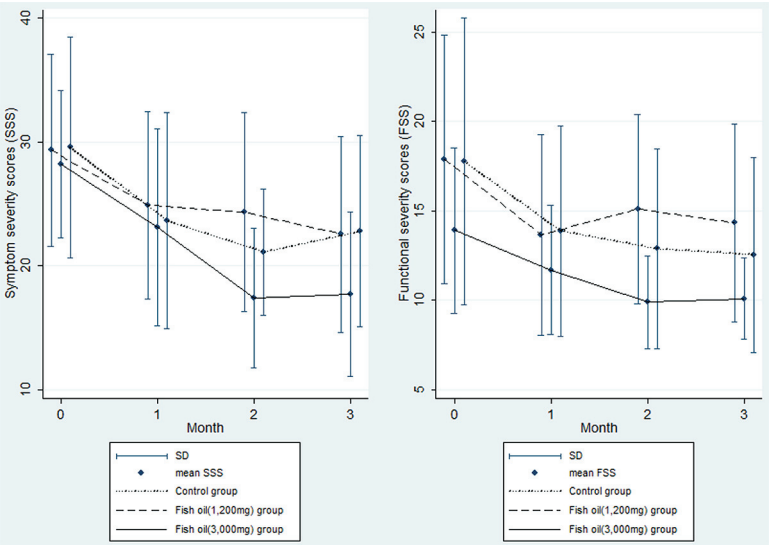

Figure 3. Symptom severity score (SSS) and functional severity score (FSS).

10 patients (16 symptomatic hands) in the fish oil 3,000 mg group and 9 patients (13 symptomatic hands) in the control group (Figure 1). The patients were recruited and followed up from March 2017 to December 2018. Demographic and baseline characteristics of the patients did not statistically have significant differences, except the duration of symptoms (p=0.042) (Table 1). There was a statistically significant difference (p=0.016) in the duration of symptoms between the fish oil 3,000 milligrams group and the control group.

The NRS scores for numbness and pain were significantly reduced in the first, second and third month in the fish oil 1,200 mg group and the fish oil 3,000 mg group compared with the baseline. In the control group, the NRS score for numbness was significantly reduced in the second and third month but there was no significant change in the NRS score for pain compared with the baseline. The SSS was significantly reduced in the first, second and third month in the fish oil 1,200 mg group, the fish oil 3,000 mg group, and the control group compared

Table 2. Comparison of treatment outcome within group

Outcome variable	Fish oil 1,200 mg group n=9/ hand=13		Fish oil 3,000 mg group n=10/ hand=16		Control group n=9/ hand=13	
	Mean±SD	p-value (within group)	Mean±SD	p-value (within group)	Mean±SD	p-value (within group)
NRS for numbness						
Baseline	6.4±2.8		5.8±2.6		5.5±2.3	
1st month	4.0±2.2	<0.001*	3.9±3.0	0.002*	4.5±2.7	0.219
2nd month	4.9±2.5	0.012*	2.1±2.5	<0.001*	3.9±1.4	0.047*
3rd month	3.5±1.6	<0.001*	2±2.6	<0.001*	3.5±2.4	0.014*
NRS for pain						
Baseline	4.4±3.3		4.1±3.1		3.2±3.0	
1st month	1.8±2.1	<0.001*	2.1±2.3	0.007*	2.9±3.0	0.626
2nd month	2.9±2.6	0.017*	1±1.6	<0.001*	2.2±1.8	0.205
3rd month	1.7±2.3	<0.001*	1±2.0	<0.001*	3.3±2.6	0.922
SSS						
Baseline	29.3±7.8		28.2±5.9		29.6±8.9	
1st month	24. 9±7.6	0.012*	23.1±7.9	0.012*	23.7±8.7	0.012*
2nd month	24.3±8.0	0.005*	17.4±5.6	<0.001*	21.1±5.1	<0.001*
3rd month	22.6±7.9	<0.001*	17.7±6.6	<0.001*	22.8±7.7	0.004*
FSS						
Baseline	17.9±6.9		13.9±4.6		17.8±8.0	
1st month	13.7±5.6	0.012*	11.7±3.6	0.012*	13.9±5.9	0.032*
2nd month	15.1±5.3	0.100	9.9±2.6	<0.001*	12.9±5.6	0.007*
3rd month	14.3±5.6	0.035*	10.1±2.3	<0.001*	12.6±5.5	0.004*

NRS=numeric rating scale; SSS=symptom severity score; FSS=functional severity score; SD=standard deviation

* Statistical significance, p<0.05

with the baseline. The FSS was significantly reduced in the first and third month in the fish oil 1,200 mg group compared with the baseline. The FSS was significantly reduced in the first, second and third month in the fish oil 3,000 mg group and the control group compared with the baseline (Figure 2, 3; Table 2).

A comparison of treatment outcomes between groups is shown in Table 3. The mean difference of NRS scores for numbness and pain were significantly reduced every month in the fish oil 3,000 mg group compared with the control group (numbness: mean difference –0.6, 95% CI –1.2 to –0.1, p=0.017; pain: mean difference –0.8, 95% CI –1.3 to –0.2, p=0.005). For the fish oil 1,200 mg group compared with the control group, the mean difference of NRS scores were also reduced every month but without statistically significant difference. The SSS and FSS did not indicate statistically significant difference in either the fish oil 1,200 mg group compared with the control group or the fish oil 3,000 mg group compared with the control group.

The electrodiagnostic CTS severity remained the same in most of the samples in each group. There was no statistically significant difference among groups (Table 4).

Minor gastrointestinal side effects, including heartburn and abdominal discomfort, were found in two patients in the fish oil 1,200 mg group, three patients in the fish oil 3,000 mg group, and two patients in the control group without statistical significant difference (p=1.000). Serious side effects were not found in any of the patients.

Discussion

The present study showed a decrease in the fish oil 1,200 mg and 3,000 mg groups in terms of the numbness score, pain score, SSS, and FSS compared with the baseline in each group until the follow-up three months later. The treatment was effective in the fish oil 3,000 mg group, with significant reductions in the numbness and pain scores every month compared with the control group. Electrodiagnostic results

Table 3. Comparison of treatment outcomes between groups

Outcome variables	Fish oil 1,200 mg group vs. Control group			Fish oil 3,000 mg group vs. Control group		
	Mean difference for every month	p-value	95% CI	Mean difference for every month	p-value	95% CI
NRS for numbness	−0.01	0.957	−0.6 to 0.5	−0.6	0.017*	−1.2 to −0.1
NRS for pain	−0.5	0.109	−1.0 to 0.1	−0.8	0.005*	−1.3 to −0.2
SSS	0.4	0.685	−1.4 to 2.1	−1.4	0.121	−3.1 to 0.4
FSS	0.7	0. 305	−0.7 to 2.2	0.3	0.624	−1.0 to 1.7

NRS=numeric rating scale; SSS=symptom severity score; FSS=functional severity score; CI=confidence interval

Linear mixed effect models with adjustment for duration of symptoms were used

* Statistical significance, p<0.05

Table 4. Change of electrodiagnostic CTS severity

Severity degree	Fish oil 1,200 mg group, n=9/hand=13 n (%)	Fish oil 3,000 mg group, n=10/hand=16 n (%)	Control group, n=9/hand=13 n (%)	p-value
Better	3 (23)	2 (12)	1 (8)	0.810
Same	7 (54)	11 (69)	10 (77)	
Worse	3 (23)	3 (19)	2 (15)	

CTS=carpal tunnel syndrome

revealed that the degree of severity did not change in most of the patients in each group after three months.

The numbness score, pain score, SSS, and FSS in both fish oil groups significantly decreased compared with the baseline. Omega-3 fatty acids have various mechanisms to stimulate nerve recovery and reduce pain. They enhance remyelination and stimulate nerve recovery via microglial M1 inhibition and microglial M2 activation[23,24]. Omega-3 fatty acids reduce the nociceptive pain via inflammatory cytokine reduction and transient receptor potential vanilloid 1 (TRPV1) inhibition[25-29]. Furthermore, DHA indirectly stimulates an endogenous opioid peptide β-endorphin release that increases pain modulation pathway[30]. Omega-3 fatty acids block the activity of mitogen-activated protein kinase and block voltage-gated sodium channels (VGSCs) to reduce neuropathic pain[31-33]. The results of the present study indicate that the intake of omega-3 fatty acids at the level of 3,000 mg per day was effective as it significantly reduced numbness and pain scores every month compared with the control group. The effective dosage in the present study was equal to that of a previous case report study on the treatment of CTS with omega-3 fatty acids[20]. However, the effective dosage was higher than that of a previous study on the treatment of non-surgical neck or back pain that used omega-3 fatty acids at 1,200 mg per day[17]. The intake of omega-3 fatty acids at the level of 3,000 mg per day was more effective than the 1,200 mg per day level because CTS involved both an inflammatory process and nerve demyelination. Nevertheless, the SSS and FSS in the control group significantly decreased compared with the baseline. The SSS and FSS are sensitive to clinical change and influenced by physician-patient communication, illness perception, anxiety, and depression levels[34-36]. All patients received knowledge and management about CTS that could reduce the SSS and FSS score in the control group.

Electrodiagnostic results revealed that the degree of severity did not change in most of the patients in all three groups after three months. Similarly, a case report study on CTS treatment with 3,000 mg per day of omega-3 fatty acids also found no changes in the degree of severity after eight months. They showed distal sensory and motor latency reduction and motor amplitude improvement of median NCS[20]. Nerve recovery usually requires a great amount of time even after patient symptoms have improved. A previous study showed that CTS symptoms did not correlate with NCS[37].

Due to the safety of omega-3 fatty acids, the patients were administered 1,200 and 3,000 mg per day. The patients experienced some gastrointestinal problems, such as heartburn and abdominal discomfort, but to a tolerable degree. Their symptoms subsided when they immediately took fish oil after a meal. Like

the present study, the previous randomized controlled trial (RCT) study used omega-3 fatty acids at 3,360 mg per day versus placebo. Gastrointestinal and musculoskeletal complaints were reported but there were no significant differences between groups and symptoms were tolerable[38]. No serious side effects were found in the patients.

One limitation of the present study was the duration of symptoms that was a statistically significant difference in baseline characteristics. The prolonged duration of symptom might delay the median nerve recovery that affected the outcomes of treatment. The authors used a linear mixed-effect model to adjust this factor and to analyze the outcomes. Another limitation was low power to detect difference in secondary outcomes. As a solution, a larger number of participants should be enrolled to reduce difference in baseline characteristics and increase power to detect difference in secondary outcomes in the future study.

Conclusion

Omega-3 fatty acids (EPA/DHA 3,000 mg per day) reduce numbness and pain with statistically significant difference in treatment of mild to moderate CTS. However, clinical significance was still in doubt and need further research to explore. Omega-3 fatty acids 1,200 and 3,000 mg are safe to use.

What is already known on this topic?

Omega-3 fatty acids (EPA/DHA) are widely used as supplements for anti-inflammation, pain reduction and nerve remyelination. Omega-3 fatty acids were studied in the treatment of non-surgical neck or back pain, rheumatoid arthritis, cervical radiculopathy, and multiple sclerosis.

What this study adds?

Fish oil consisting of omega-3 fatty acids 3,000 mg per day, plus vitamin B, was effective and significantly reduced numbness and pain scores every month compared with vitamin B supplement alone.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Aboonq MS. Pathophysiology of carpal tunnel syndrome. Neurosciences (Riyadh) 2015;20:4-9.
2. Suwannawong N, Teeranet G, Rukhamet B. The prevalence of impaired sensory conduction of the median nerve at the carpal tunnel in computer occupational setting people. J Thai Rehabil Med 2001;10:100-6.
3. Franklin GM, Friedman AS. Work-related carpal tunnel syndrome: Diagnosis and treatment guideline. Phys Med Rehabil Clin N Am 2015;26:523-37.
4. Durka-Kesy MA, Pastuszak Z, Tomczykiewicz K, Maciagowska-Terela M, Stepien A. The duration of the symptoms of carpal tunnel syndrome to the diagnosis. Pol Merkur Lekarski 2014;37:338-40.
5. Chammas M, Boretto J, Burmann LM, Ramos RM, Dos Santos Neto FC, Silva JB. Carpal tunnel syndrome - Part I (anatomy, physiology, etiology and diagnosis). Rev Bras Ortop 2014;49:429-36.
6. Jesus Filho AG, do Nascimento BF, Amorim MC, Naus RA, Loures EA, Moratelli L. Comparative study between physical examination, electroneuromyography and ultrasonography in diagnosing carpal tunnel syndrome. Rev Bras Ortop 2014;49:446-51.
7. Piazzini DB, Aprile I, Ferrara PE, Bertolini C, Tonali P, Maggi L, et al. A systematic review of conservative treatment of carpal tunnel syndrome. Clin Rehabil 2007;21:299-314.
8. Huisstede BM, Friden J, Coert JH, Hoogvliet P. Carpal tunnel syndrome: hand surgeons, hand therapists, and physical medicine and rehabilitation physicians agree on a multidisciplinary treatment guideline-results from the European HANDGUIDE Study. Arch Phys Med Rehabil 2014;95:2253-63.
9. Holm G, Moody LE. Carpal tunnel syndrome: current theory, treatment, and the use of B6. J Am Acad Nurse Pract 2003;15:18-22.
10. Ryan-Harshman M, Aldoori W. Carpal tunnel syndrome and vitamin B6. Can Fam Physician 2007;53:1161-2.
11. Shi Q, MacDermid JC. Is surgical intervention more effective than non-surgical treatment for carpal tunnel syndrome? A systematic review. J Orthop Surg Res 2011;6:17.
12. Baker NA, Livengood HM. Symptom severity and conservative treatment for carpal tunnel syndrome in association with eventual carpal tunnel release. J Hand Surg Am 2014;39:1792-8.
13. Tokuyama S, Nakamoto K. Unsaturated fatty acids and pain. Biol Pharm Bull 2011;34:1174-8.
14. Calder PC. Functional roles of fatty acids and their effects on human health. JPEN J Parenter Enteral Nutr 2015;39(1 Suppl):18S-32S.
15. Nordvik I, Myhr KM, Nyland H, Bjerve KS. Effect of dietary advice and n-3 supplementation in newly diagnosed MS patients. Acta Neurol Scand 2000;102:143-9.

16. Michael-Titus AT. Omega-3 fatty acids and neurological injury. Prostaglandins Leukot Essent Fatty Acids 2007;77:295-300.
17. Maroon JC, Bost JW. Omega-3 fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain. Surg Neurol 2006;65:326-31.
18. Park Y, Lee A, Shim SC, Lee JH, Choe JY, Ahn H, et al. Effect of n-3 polyunsaturated fatty acid supplementation in patients with rheumatoid arthritis: a 16-week randomized, double-blind, placebo-controlled, parallel-design multicenter study in Korea. J Nutr Biochem 2013;24:1367-72.
19. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 2007;129:210-23.
20. Ko GD, Nowacki NB, Arseneau L, Eitel M, Hum A. Omega-3 fatty acids for neuropathic pain: case series. Clin J Pain 2010;26:168-72.
21. Upatham S, Kumnerddee W. Reliability of Thai version Boston questionnaire. J Med Assoc Thai 2008;91:1250-6.
22. Stevens JC. AAEM minimonograph #26: the electrodiagnosis of carpal tunnel syndrome. American Association of Electrodiagnostic Medicine. Muscle Nerve 1997;20:1477-86.
23. Chen S, Zhang H, Pu H, Wang G, Li W, Leak RK, et al. n-3 PUFA supplementation benefits microglial responses to myelin pathology. Sci Rep 2014;4:7458.
24. Gladman SJ, Huang W, Lim SN, Dyall SC, Boddy S, Kang JX, et al. Improved outcome after peripheral nerve injury in mice with increased levels of endogenous omega-3 polyunsaturated fatty acids. J Neurosci 2012;32:563-71.
25. Rupp H, Wagner D, Rupp T, Schulte LM, Maisch B. Risk stratification by the "EPA+DHA level" and the "EPA/AA ratio" focus on anti-inflammatory and antiarrhythmogenic effects of long-chain omega-3 fatty acids. Herz 2004;29:673-85.
26. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol 2008; 8:349-61.
27. Bagga D, Wang L, Farias-Eisner R, Glaspy JA, Reddy ST. Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. Proc Natl Acad Sci U S A 2003;100:1751-6.
28. Mirnikjoo B, Brown SE, Kim HF, Marangell LB, Sweatt JD, Weeber EJ. Protein kinase inhibition by omega-3 fatty acids. J Biol Chem 2001;276:10888-96.
29. Matta JA, Miyares RL, Ahern GP. TRPV1 is a novel target for omega-3 polyunsaturated fatty acids. J Physiol 2007;578:397-411.
30. Nakamoto K, Nishinaka T, Ambo A, Mankura M, Kasuya F, Tokuyama S. Possible involvement of beta-endorphin in docosahexaenoic acid-induced antinociception. Eur J Pharmacol 2011;666:100-4.
31. Shapiro H. Could n-3 polyunsaturated fatty acids reduce pathological pain by direct actions on the nervous system? Prostaglandins Leukot Essent Fatty Acids 2003;68:219-24.
32. Xiao YF, Kang JX, Morgan JP, Leaf A. Blocking effects of polyunsaturated fatty acids on Na+ channels of neonatal rat ventricular myocytes. Proc Natl Acad Sci U S A 1995;92:11000-4.
33. Hong MP, Kim HI, Shin YK, Lee CS, Park M, Song JH. Effects of free fatty acids on sodium currents in rat dorsal root ganglion neurons. Brain Res 2004;1008: 81-91.
34. Padua L, Padua R, Aprile I, Caliandro P, Tonali P. Boston carpal tunnel questionnaire: the influence of diagnosis on patient-oriented results. Neurol Res 2005;27:522-4.
35. Sun PO, Walbeehm ET, Selles RW, Jansen MC, Slijper HP, Ulrich DJO, et al. Influence of illness perceptions, psychological distress and pain catastrophizing on self-reported symptom severity and functional status in patients with carpal tunnel syndrome. J Psychosom Res 2019;126:109820.
36. Khan F, Shehna A, Ramesh S, Sandhya KS, Paul R. Subjective symptoms of carpal tunnel syndrome correlate more with psychological factors than electrophysiological severity. Ann Indian Acad Neurol 2017;20:69-72.
37. Sevinc EG, Tekesin A, Tunc A. Evaluation of symptom severity, functional status and anxiety levels in patients with carpal tunnel syndrome with different electrophysiological stages. Ideggyogy Sz 2018;71: 417-22.
38. de Ferranti SD, Milliren CE, Denhoff ER, Steltz SK, Selamet Tierney ES, Feldman HA, et al. Using high-dose omega-3 fatty acid supplements to lower triglyceride levels in 10- to 19-year-olds. Clin Pediatr (Phila) 2014;53:428-38.