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Original Research Article

The Role of Omega-3 EPA/DHA Oral Soft gel in The Treatment of Stable Bronchiectasis

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Abstract

The omega 3 has a known anti-inflammatory effect which can be beneficial in many human diseases in the respiratory & other systems.
In respiratory system its role is not mature yet as in asthma, COPD & bronchiectasis & most are still under study.
The safety issues also need to be addressed in the treatment with a relatively need medication.
To evaluate the use of omega-3 EPA/DHA oral softgel in the treatment of stable (not in exacerbation) bronchiectasis regarding safety/efficacy effect.
44 Patients with stable bronchiectasis are randomly assigned to the active group (participants receive omega-3 EPA/DHA oral softgel (EPA 180mg &DHA 120mg) once daily for 6 months in addition to their usual treatment) or the control group (participants receive the usual treatment only for 4 months) from January 2013 to march 2016.
Interventional randomized parallel assignment study concern in the safety /efficacy of a suggested treatment.
Omega 3 can used in patients with stable bronchiectasis with the expected benefits:
1- reduce exacerbation rate
2- improve FEV1
3- may improve CAT scoreThe treatment does not cause serious side effects regarding the safety aspect apart from the fishy odor sensed by the patients .

Key Words: omega 3 EPA/AHA oral softgel, bronchiectasis, acute exacerbation, antioxidant, anti-inflammatory.

دور دواء الاوميكا 3 (الكبسول المرن) في علاج حالات توسع القصبات المستقر

الخلاصة

اوميغا 3 له تأثيراته المعروفة المضادة للالتهابات التي يمكن أن تكون مفيدة في كثير من الأمراض التي تصيب الإنسان في الجهاز التنفسي وغيرها من النظموان دورها في الجهاز التنفسي لم يتضح بشكل كامل بعد كما في الربو ومرض التهاب القصبات المزمن و توسع القصبات ومعظمها لا يزال قيد الدراسة، كما ان قضايا السلامة تقتضيأيضا حساباتاستخدام علاج ذو فائدة نسبية. لتقييم استخدام الأوميغا 3 عن طريق الفم في علاج مرض توسع القصبات المستقر (وليس تلك التي تحصل بشكل نوبة) بشأن السلامة.

تم تقسيم44 المرضى الذين يعانون من توسع القصبات المستقرة بشكل عشوائي على مجموعة نشطة (يتلقى المشاركون أوميغا 3- (EPA 180mgو DHA 120mg) مرة واحدة يوميا لمدة 6 أشهر بالإضافة إلى علاجهم المعتاد) أو المجموعة الاخرى (يتلقى المشاركون العلاج المعتاد

فقط لمدة 6 أشهر) خلال الفترة من يناير 2013 إلى اذار 2016. أوميغا 3 يمكن استخدامها في المرضى الذين يعانون من توسع القصبات مستقرة مع الفوائد المتوقعة :1- خفض معدل تفاقم، 2- تحسينFEV1 ، 3- قد يحسن النتيجةCAT.
كما ان العلاج لايسبب آثار جانبية خطيرة فيما يتعلق بجانب السلامة ما عدا حصولرائحة غير مريحة (رائحه سمك في الفم) وجدت من قبل بعض المرضى.

الكلمات المفتاحية :أوميغا 3,الكبسول المرن الفموي، توسع القصبات، تفاقم حاد في توسع القصبات، مضادات للأكسدة.

Introduction

Animal and human studies have identified the long-chain n-3 polyunsaturated fatty acids (n-3 PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as the likely major active constituents in fish oil [1].

In randomized trials, fish oil supplementation improves several human diseases risk factors as hypertriglyceridemia and dyslipidemia[2].

Mechanism of its action: mainly we will concentrate on its anti-inflammatory effect ,Potential anti-inflammatory effects of fish oil have received much attention in review articles , given the role of EPA and DHA as precursors to specific eicosanoids and other inflammatory mediators [3].

Controlled trials have generally not detected significant effects of fish oil intake on C-reactive protein levels [4]. Conversely, fish oil supplementation does appear to inhibit production of cytokines, including interleukin-1beta and tumor necrosis factor-alpha [5]. However, this effect may be dose related and it is not clear whether lower doses produce substantial anti-inflammatory effects [6].

Many randomized trials in humans have demonstrated that fish oil consumption also lowers circulating markers of endothelial dysfunction, such as E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) [7,8].

Experimental evidence suggests that other metabolites of EPA and DHA, including resolvins, protectins, and maresins, may play crucial roles in active resolution of inflammation [9]. In animal models, these metabolites protect a range of tissues from the adverse effects of acute inflammatory insults [10].Beneficial roles include:

Its role is nearly established in cardiovascular and neurological systems defects as MI, hypertension, strokes, arrhythmias, dementia & depression [11].

In respiratory system its role is not mature yet, in asthma: Diets rich in anti-inflammatory omega-3 fatty acids have been proposed to be beneficial in the treatment of asthma. A systemic review of the literature was difficult to find any evidence of benefit, although this was largely attributable to inconsistency in study design and measures of respiratory outcomes [12]. Subsequent to this analysis, one study demonstrated positive effects of omega-3 fatty acids (fish oil supplements) in patients with exercise-induced bronchoconstriction (EIB)[13]. The group on fish oil supplements had reduced leukotriene, PGD2, IL-1 beta, and TNF alpha in induced sputa[14]. Pulmonary function improved and bronchodilator use was reduced. This suggests that a diet enriched with omega-3 fatty acids may be helpful in asthmatics with EIB, a finding that warrants further study [15].

Safety and side effects:

In a pooled analysis of randomized clinical trials, the most common side effects of fish oil consumption were gastrointestinal disturbances such as nausea, occurring in approximately 4-20% depending on the dose [16].

Perhaps the most common symptom causing discontinuation of fish oil supplements is "fishy taste" following eructation [17].

Safety — In small trials, fish oil capsules up to 12 g /day (containing 6 g /day n-3 PUFA) have been administered for more than 2 years without serious adverse events [18].

Although even these very high doses of fish oil appear to be safe, total intakes up to 3 g

per day of EPA and DHA are Generally Recognized As Safe [19] but higher dosing should generally be under the guidance of a clinician.

Bleeding — the mechanism of bleeding is in patients who take fish oil supplements, the omega-3 fatty acids compete with arachidonic acid (20:4n-6) for incorporation into the platelet cell membranes, so the preference is shifted towards a greater degree of prostaglandin I_2production which has local vasodilatory and antiplatelet effects. In addition, there is less formation of TXA_2 and platelet activating factor which are both known to activate platelets.

All of these effects translate to increases in bleeding time and a reduction in ADP, collagen and epinephrine induced platelet aggregation in patients taking omega-3 fatty acid supplements.

There is probably no clinically significant effect on bleeding risk. Risk of bleeding was evaluated in nine trials including 2612 participants, including individuals taking aspirin or warfarin . No bleeding was seen in four trials, and in the other five trials no consistent associations were seen between fish oil dose and bleeding risk [20].

Materials and Methods

The aim of the study to evaluate the use of omega-3 EPA/DHA oral softgel in the treatment of stable bronchiectasis regarding safety/efficacy effect.

Methods

44 Patients with stable bronchiectasis will be randomly assigned to the active group (participants receive omega-3 EPA/DHA oral softgel (EPA 180mg &DHA 120mg) once daily for 6 months in addition to their usual treatment) or the control group (participants receive the usual treatment only for 6 months).

Study duration: from January 2013 to march 2016

Study design: interventional randomized parallel assignment study concern in the safety /efficacy of a suggested treatment

Eligibility

Ages eligible for Study:	15 Years to 70 Years(as the diseases seen in wide range of age)
Genders eligible for Study:	Both

Criteria

Inclusion Criteria:

- Confirmed diagnosis of bronchiectasis by chest HRCT
- Stable Bronchiectasis or one month after the acute exacerbation of bronchiectasis

Exclusion Criteria

- Recent or active Smokers within 6 months
- if associated with bronchial asthma
- Have any serious or active medical or psychiatric illness.

Study endpoints:

- **Primary Outcome Measures:**

Acute exacerbations: an exacerbation of bronchiectasis is defined as either a change in one or more of the common symptoms of bronchiectasis (sputum volume or purulence, dyspnea and cough) or the onset of new symptoms (fever, pleurisy, hemoptysis) or need for antibiotic treatment.

- **Secondary Outcome Measures:**
  - Chronic Obstructive Pulmonary Disease Assessment Test (CAT) :as <5 normal, 5-10 m low impact ,10-20 medium impact, 20-30 high impact, >30 very high impact
  - Change in forced expiratory volume in one second (FEV1) (Percent of Predicted for Age)

Safety issues:

- adverse Events :Wt. loss, bleeding tendency ,GI upset & bad retched odor

Results and Discussion

Table1: Distribution of patients according to age and gender.

Age (years)	(44.13± 7.41)	(30-57)
Gender		
Male	31	70.5%
Female	13	29.5%
Total	44	100.0%

The mean age is 44.13 mean that the disease affect the persons at their active period which make the disease a social & financial problem in addition to be a medical one.

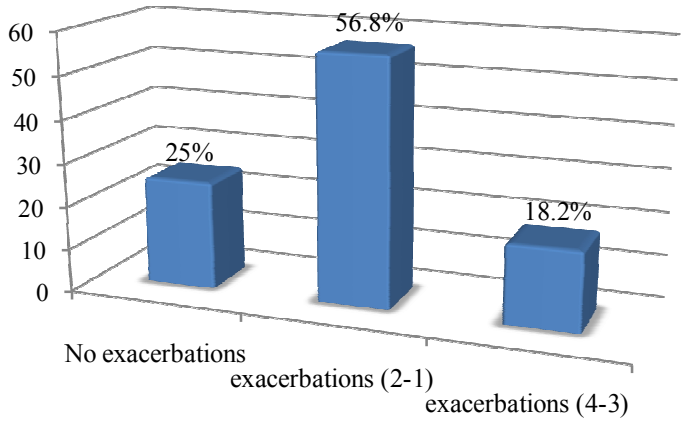

Figure 1:Distribution of all patients with bronchiectasis according to frequency of exacerbations during period of 6 months.

It show that the majority develop 1-2 attacks of exacerbations over the study period which indicate the relapsing nature of the disease as expected

Table 2: Distribution of patients according to side effects including (weight loss, bleeding, gastrointestinal upset and bad retching).

Side effects	**No.**	**%**
Weight loss		
Yes	10	22.7%
No	34	77.3%
Total	44	100.0%
Bleeding		
Yes	0	0.0%
No	44	100.0%
Total	44	100.0%
Gastrointestinal upset		
Yes	20	45.5%
No	24	54.5%
Total	44	100.0%
Bad retching		
Yes	17	38.6%
No	27	61.4%
Total	44	100.0%

The above table show that the side effects were reported in all patients in both arms which indicate that the bronchiectasis has some systemic effects by itself

Table 3 Mean differences of age (years) by the study groups

Variable	Study groups	N	Mean ± SD	t-test	P-value
Age (years)	Group 1 (regular use omega 3)	22	44.81 ± 6.95	0.605	0.548
	Group 2 (not use omega 3)	22	43.45 ± 7.96		

Table 4 Mean differences of gender by the study groups

Gender	Group 1	Group 2	χ^2	P-value
Male	16 (72.7)	15 (68.2)	**0.109**	**0.741**
Female	6 (27.3)	7 (31.8)		
total	22	22		

Results found that both groups were matched in age and gender

Table 5 Association between study groups including (patients with regular use of omega 3 and comparison group) and the primary end points (frequency of exacerbations during period of follow up).

Study variables	Study Groups		χ^2	P-value
	Use omega 3	Not use		
Number of exacerbations				**0.035*[a]**
No exacerbation	9 (40.9)	2 (9.1)		
(1-2) exacerbations	11 (50.0)	14 (63.6)		
(>3) exacerbations	2 (9.1)	6 (27.3)		

Showing a statistically significant differences in the rate of exacerbations with the use of omega 3 & this result is consistent with the theoretical base of the study.

By comparing with local or national studies , there were no similar studies in our region for comparison as the subject is a bit new & not clear enough yet.

Table 6 Association between study groups and side effects including (weight loss, gastrointestinal upset and bad retching) during 6 months period of follow up.

Side effects	Study Groups		χ^2	P-value
	Use omega 3	Not use		
Weight loss Present Absent	 3 (13.6) 19 (86.4)	 7 (31.8) 15 (68.2)	2.071	0.15
GIT upset Present Absent	 10 (45.5) 12 (54.5)	 10 (45.5) 12 (54.5)	0.000	1.000
Bad retching Present Absent	 13 (59.1) 9 (40.9)	 4 (18.2) 18 (81.8)	**7.765**	**0.005**

Regarding the safety issues there were no serious side effects reported although it need a longer duration of follow up (may be years) to observe some serious side effects as cancer.

But the only bothering side effect mention by the treated arm with a statistically significant difference from the placebo arm is bad odor retching (fishy odor) while other effects were seen in both arms.

Table 7: Mean differences of CAT score between pre and post using of omega 3.

Variable	Categories	No.	Mean	Paired t-test	P value
CAT score	Pre using	22	21.09	11.868	**<0.001****
	Post using	22	16.09		

Table 8: Mean differences of FEV1 between pre and post using of omega 3.

Variable	Categories	No.	Mean	Paired t-test	P value
FEV1	Pre using	22	55.5	-13.457	**<0.001****
	Post using	22	63.00		

Table 9: Mean differences of CAT score by study groups including (patients with regular use of omega 3 and comparison group not use that drug) after 6 months of follow up.

Variable	Study groups	N	Mean ± SD	t-test	P value
CAT score	**Group 1 (regular use omega 3)**	22	16.09 ± 6.24	-1.703	0.096
	Group 2 (not use omega 3)	22	19.59 ±7.33		

Table 10: Mean differences of FEV1 by study groups including (patients with regular use of omega 3 and comparison group not use that drug) after 6 months of follow up.

Variable	Study groups	N	Mean ± SD	t-test	P value
FEV1	Group 1 (regular use omega 3)	22	63.00 ± 8.98	2.2	0.033*
	Group 2 (not use omega 3)	22	55.77 ±12.51		

There were a significant difference regarding the CAT score and the FEV1 changes after treatment which suggest addition benefit of omega 3 but the change in CAT score does not persist when compare with the placebo arm, this may be due to short duration of follow up or small sample size

While the changes in FEV1 does persist when compare to the placebo arm which may indicate direct beneficial effect of the used medication.

Conclusion

- omega 3 can used in patients with stable bronchiectasis with the expected benefits:

1- reduce exacerbation rate
2- improve FEV1
3- may improve CAT score

- the treatment does not cause serious side effects regarding the safety aspect apart from the fishy odor sensed by the patients .

Limitation of the study

1- Cannot differentiate the specific causes of bronchiectasis
2- Cannot follow the patient for a longer period
3- The effect of other confounder as diet,types of food or exercise effect on the result

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