

Full length Research paper

A clinical-controlled trial compared carom caraway (black cumin, *Nigella sativa*) and metoclopramide in functional dyspepsia

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The treatment of patients with functional dyspepsia remains unsatisfactory. We assessed the efficacy of carom caraway (black cumin) in comparison with metoclopramide, in patients with functional dyspepsia. Outpatients who were considered functional dyspepsia (Rom II criteria) were eligible for the trial. Dyspeptic symptoms had to be present for at least 12 weeks within the preceding 12 months, without any identifiable structural disease and GERD on endoscopy. The *Helicobacter pylori* infection had been ruled out by ELISA (Enzyme-linked immunosorbent assay) antibody and urea breath test (UBT). Patients were randomly separated into two groups with block design. The study medication was packaged identically. We used 10 grades visual analog scale to assess the severity of dyspeptic symptoms before and after a two-week treatment. We used SPSS 13 software for analyzing the data, estimated odds ratio and its 95% CI, the P value (<0.05) were statistically estimated significant. 160 eligible patients were recruited, 80 in each group, 36 (45%) males in cumin and 33 (41.25%) males in metoclopramide group respectively. the mean age in the cumin group was 38.56 (SD=13.65) and in metoclopramide group, it was 36.41 (SD=12.15). The visual analog scale assessment of symptoms in pre and post treatment is shown in given. Dyspeptic symptoms in two groups after dichotomous variable changes were compared. We conclude that carom caraway has effects of similar magnitude on metoclopramide to control the symptoms of functional dyspepsia, and encourages safety profiles.

Key words: Functional dyspepsia, *Nigella sativa*, carom caraway, black cumin, metoclopramide.

INTRODUCTION

Dyspepsia is a common and costly problem in primary care and gastroenterology practice. In most patients examined, no structural lesions causing these symptoms are found. Dyspepsia, in the absence of a clinical identifiable structural lesion, is referred to as functional dyspepsia (Tack et al., 2006; Baker et al., 2006; Muller and Malferthiner, 2006; Baker et al., 2006). Pharmacological treatments for patients with functional dyspepsia remained unsatisfactory (Morin, 2006). The results of the controlled trials are generally disappointing, and only small benefits relative to placebo are found with H₂-blocker proton-pump inhibitors, and *Helicobacter pylori*

eradication (Gwee and Chua, 2006). Although several randomized, controlled clinical trials demonstrate the superiority of prokinetic (metoclopramide and cisaprid) over placebo, the use of prokinetic is now restricted in most countries because of the side effects (Abhar et al., 2003; Kantar et al., 2005, 2005 George and Spikler, 2003).

Many people prefer herbal extracts and diet modifications to chemical agents as medication to control their gastrointestinal discomfort. *Nigella sativa* (black cumin, carom caraway) extract is one of the many herbal medications commonly used in many countries. *N. sativa*, and cuminum (green cumin) are two spices of the same family of Apiaceae. *N. sativa* is an annual plant with an approximate height of 30 to 50 cm, and bluish white flowers that give rise to 5 to 6 mm capsule fruit with

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Table 1. Visual analogue scale of different pre-treatment symptoms of the studied groups.

Symptom	Cumin group		Metoclopramide group	
	Mean	Std. dev.	Mean	Std. dev.
Abdominal distention	5.95	2.89	5.70	2.76
Nausea	1.99	2.35	2.38	2.48
Early satiety	4.38	3.07	4.31	3.45
Post prandial fullness	5.21	2.99	5.56	3.11
Post prandial pain	1.94	2.91	2.14	2.85
Vomiting	0.53	1.68	0.41	0.98

seeds inside. The extract of these seeds is made up of many different substances such as paracimole Alpha and Beta, chromic Aldeid Alpha and Beta, Terpeneol flandron, and Odenol Oil (George and Spikler, 2003).

In ancient times, this plant was brought from Egypt (its origin) to Asia and Iran. Nowadays, it is used as a spice and also as a medicine for skin lesions, antioxidant, anti-allergic, and the removal of bloating and abdominal colic's, promoting appetite and digestion and as an anti diarrhea agent (constipating agent) (Hosinie, 2004).

However, many herbal extracts have traditionally been used for the treatment of abdominal discomfort, pain and dyspepsia in many countries. The pharmacological insights into their effects on the functional dyspepsia are poor (Firooznia and Bigdeli, 2004; Zargari, 1997; Zanaty et al., 2004; Fraise and Kohler, 1999; Madisch et al., 1999; Thompson and Ernst (2002) Holtmann et al., 1999; Sassin and Buchert, 2000; Dobrilla et al., 1989; Moayyedi et al., 2000; Eenst et al., 1998) In Iran, black and green cumin seeds and extracts are used for many different abdominal discomforts but the controlled clinic pharmacological trial on the effect of cumin is very rare (George and Spikler, 2003; Hosinie, 2004; Saberi et al., 2004). The objective of this study is to compare the effects of black cumin versus metoclopramide on patients with functional dyspepsia.

METHODS

Study design and patient population

Outpatients who were considered to have functional dyspepsia on the basis of the Rome III criteria were eligible for the trial. Abdominal discomfort symptoms like pain, post prandial fullness, bloating, nausea, and early satiety had to be present for at least 12 weeks within the preceding 12 months, without any identifiable structural disease on endoscopy. H. pylori infection was ruled out by ELISA antibody and urea breathe test (UBT). Patients who had predominantly reflux-related symptoms were not eligible for participation. Patients were recruited by Arak Medical University Gastroenterology Clinics. Before the patients were included in the trial, they were taken under physical and laboratory tests for FBS

(Fetal bovine serum), CBC (complete blood count), LFT (Liver function tests) abdominal Sonography, H. pylori ELISA antibody and UBT. Upper GI endoscopies were done to rule out structural causes for the symptoms. Patients having problems such as: Taking other drugs, being pregnant, COPD (Chronic obstructive pulmonary disease), CHF (Chronic heart failure), BMI (body mass index) > 27, being smokers (habitual smoking) or addict, and also having collagen vascular diseases, and cirrhotic; were excluded from the study. The study was approved and supported by the Ethical Committee of the Iran-Arak Medical University.

Randomization and blinding

The recruited patients were randomly separated into two groups using randomized block design with 2 cases in each block. The study medication was packaged identically for both groups and was identifiable in screening phase. All patients applied an informed consent by which they were informed for participation in the study.

Assessment

We used visual analogue scale (with 10 grades) to assess the severity of dyspeptic symptoms (that is, nausea, vomiting, postprandial fullness, early satiety, bloating and pain) before the treatment and 2 weeks after it in each group of cumin and metoclopramide. The assessment was performed by a trained physician who was unaware of the kind of treatment (Carlson, 1983; Deloach et al., 1998; Soyannwo, 2000).

Statistical analysis

In order to compare the results of the two groups, we used Mann-Whitney-U test as well as estimation of odds ratio and its 95% confidence interval. The p values of < 0.05 were statistically estimated significant. We used SPSS (13) software for analyzing our data.

RESULTS

160 eligible patients were recruited in the study (80 of them in cumin and 80 in metoclopramide group). 69 patients were males (43.1%) and 91 were females (56.9%). 36 males were recruited in the cumin group (45%). This figure was about 33 (41.25%) males in the metoclopramide. The mean age of the patients in the cumin group was 38.56 (SD=13.65) and in metoclopramide, it was 36.41 (SD=12.15). 'The visual analogue scales' of pretreatment symptoms in the 2 groups are shown in Table 1. The figures after the treatment were assessed and the results are shown in Table 2.

In order to compare the prevalence of each dyspeptic symptom in the two groups of treatment, we changed the visual analogue scale of each group after treatment symptoms to a dichotomous variable. In this way, we considered those symptoms with 0 scales as not having the symptoms and other scales as having them. The result of the comparison of the two groups is shown in Table 3.

Table 2. Visual analogue scale of different post-treatment symptom of the studied groups.

Symptom	Cumin group		Metoclopramide group		P value
	Mean	Std. deviation	Mean	Std. deviation	
Abdominal distention	3.46	2.09	3.60	2.03	0.53
Nausea	1.25	1.52	1.68	1.85	0.32
Early satiety	2.66	2.12	2.61	2.31	0.84
Postprandial fullness	3.19	2.08	3.53	2.30	0.44
Post prandial pain	1.05	1.90	1.34	2.10	0.35
Vomiting	0.35	1.40	0.28	0.62	0.40

Table 3. The comparison of the prevalence of the symptoms in the 2 groups.

Presence of symptom	Cumin group (%)	Metoclopramide group (%)	Odds ratio (95% CI)	P value
Abdominal distention	72 (90)	73 (90.3)	1.16 (0.40-3.62)	0.79
Nausea	37 (46.3)	42 (52.5)	1.28 (0.69-2.39)	0.43
Early satiety	60 (75)	57 (71.3)	0.83 (0.41-1.66)	0.59
Post prandial fullness	69 (86.3)	73 (91.3)	1.66 (0.61-4.53)	0.32
Post prandial pain	27 (33.8)	37 (46.3)	1.69 (0.89-3.20)	0.11
Vomiting	8 (10)	16 (20)	2.25 (0.90-5.61)	0.08

DISCUSSION

Disturbances in gastrointestinal motility and sensory function are now believed to play a key role in the development of symptoms in patients with functional dyspepsia. Several herbal medicinal products have been identified to be used in the relief of symptoms of non-ulcer dyspepsia. Most trial subjects treated with herbal products showed some degree of improvement in symptom scores. In many trial combinations, products of two or more herbal extracts were used. Yet it is not clear which herb is more effective (Holtmann et al., 1999; Sassin and Buchert, 2000; Dobrilla et al., 1989; Moayyedi et al., 2000; Eenst et al., 1998). In our study, we used validated 'visual analog scale' for scoring symptoms and the assessment of patients' responses. We assessed and compared the effects of black cumin powder as a single agent on metoclopramide to control the symptoms of functional dyspepsia. In this two-week study, black cumin seemed to have no clinical difference with metoclopramide in the improvement of symptoms in patients with functional dyspepsia.

George and Spikler (2003) in a clinical trial, compared the pharmaco-dynamic effects of peppermint oil and carom caraway oil with cisaprid and butylscopolamine and placebo on stomach, gall-bladder and on the oro-caecal transit time. They concluded that peppermint and carom caraway oil showed a relaxing effect on the gall-bladder and slowed down the small intestine transit time (Holtmann et al., 1999).

In several other studies, different methods have been used for scoring symptoms and not all of them have been validated techniques: Patients' entrance to trial has been

variable and it has not been clarified whether the patients with predominant reflux or *H. pylori* infection were excluded or not (Holtmann et al., 1999; Sassin and Buchert, 2000; Dobrilla et al., 1989; Moayyedi et al., 2000; Eenst et al., 1998; Carlson, 1983; Deloach et al., 1998; Soyannwo 2000).

In this study, the subjects were clearly selected for the motility type of functional dyspepsia. *H. pylori* positives and those found to have organic diseases in endoscopies were excluded.

In our study, the control group (metoclopramide) was partly intolerant, (extra pyramidal syndromes, and somnolence 12.5%). In the case group (cumin), 2.5% urticaria and 3.75% heat intolerance were observed.

The limitation of this trial was that there was no placebo arm. Comparative and placebo-controlled trials like our experience suggest cumin to be more effective than placebo and as effective as prokinetics. The safety profile and lower cost of this herb, compared with pharmacological agents, seems to be encouraging since it had been used extensively in traditional medication and culinary practices around the world (Dobrilla et al., 1989; Moayyedi et al., 2000; Eenst et al., 1998; Carlson, 1983; Deloach et al., 1998; Soyannwo et al., 2000).

Experimental studies show that *N. sativa* (carom caraway) oil (NO) has antioxidant, gastro protective effects, and decreases lipoperoxigenase and liver enzymes in alcohol inducing gastric mucosal and liver injuries (Zanaty et al., 2004; Fraise and Kohler, 1999; Madisch et al., 1999).

Madisch et al. (1999) in randomized controlled double blind trial, compared the effects of peppermint and caraway oil combination on cisapride in patients with

functional dyspepsia. They concluded that the combination of peppermint oil and caraway oil appeared to be comparable to cisapride and provided an effective means for the treatment of functional dyspepsia.

Thompson and Ernst (2002) (Dobrilla et al., 1989) in a systemic review, studied six electronic databases and more than 60 articles, nine of which included the peppermint and caraway (black cumin) used in the management of non-ulcer dyspepsia. They concluded that patients experiencing some degree of benefit in dyspeptic symptoms were comparable to the prokinetic effects and no more adverse events with these herbs than with placebo or comparative medications, although short term clinical trials were not designed to detect rare or delayed adverse events.

Conclusion

It is concluded that some of the herbal medicinal products identified, particularly black cumin (carom caraway), have effects of similar magnitude on conventional therapies (metoclopramide) and encourage safety profiles.

In comparison to prokinetic drugs, cumin can be a suitable and reasonable alternative treatment for motility dyspepsia due to its low price, availability, and also its fewer side effects.

For such a case, it is recommended to conduct further warrant investigations, especially, long term double blind clinical trial with placebo arm involving greater sample numbers to elucidate the effectiveness and importance of herbal drugs like black cumin to control functional dyspepsia.

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