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NIGELLA SATIVA IN HYPERTENSIVE NEPHROPATHY: A RANDOMIZED CLINICAL STUDY

Pharmacology

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ABSTRACT

Nigella sativa has protective role in Chronic Kidney Disease (CKD), hypertension and diabetes mellitus. We assessed effectiveness and safety of Nigella sativa oil supplementation in patients of hypertensive nephropathy in a comparative, prospective and open label study. Group 1 (Control) received conservative management while Group 2 (Test) received Nigella sativa oil along with conservative management of hypertensive nephropathy for 12 weeks. There was amelioration in clinical features and biochemical parameters but it was more noticeable in test group. A decrease in serum creatinine, blood urea, 24-hour total urinary protein (TUP) and blood pressure level was observed along with an elevation in glomerular filtration rate (GFR) and 24-hour total urinary volume (TUV). We confirm that supplementation of Nigella sativa oil is effective and safe in preventing the advancement of disease in patients of hypertensive nephropathy.

KEYWORDS

hypertensive nephropathy, nigella sativa oil, GFR

INTRODUCTION

Hypertensive nephropathy is a common cause of Chronic Kidney Disease (CKD)**.** The rise in incidence of CKD is attributed to an aging population with increases in hypertension (HTN), diabetes and obesity. Reduced GFR and albuminuria are independently result in increase in cardiovascular and all-cause mortality (Matsushita et al., 2010, Rashidi, Sehgal, Rahman, & O'Connor, 2008). National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (2002) defined CKD as: kidney damage or GFR <60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause. According to Screening and Early Evaluation of Kidney disease (SEEK)-India cohort study, the prevalence of CKD was approximately 17.2% with ~6% have CKD stage 3 or worse. Around 1,00,000 new patients of end stage renal disease (ESRD) require renal replacement therapy (RRT) annually in India (Singh et., 2013). Uncontrolled HTN causes more rapid advancement of CKD, and is the second leading cause of ESRD in the U.S.A. (Botdorf, Chaudhary & Whaley-Connell, 2011, Segura, & Ruilope, 2011). Various guidelines confer the importance of lowering blood pressure (BP) to slow down renal disease progression and decrease cardiovascular morbidity and mortality (National Kidney Foundation's 2002, Chobanian et al., 2003, American Diabetes Association, 2012).

Therefore, it is a worthwhile to include some alternative or complimentary medicine as adjunct to conservative management for CKD to reduce the number and doses of conventional medicines. Nigella sativa has a long history as a diversely beneficial herb and nephroprotective activity has been reported in various studies (El-Shamy, Mosa, El-Nabarawy, & El- Qattan, 2011, Hadjzadeh et al., 2012, Yaman, & Balicki, 2010). Another study established that Nigella sativa oil has anti-inflammatory properties and improved kidney function (Mohtashami et al., 2011).

Thymoquinone is active component of Nigella sativa which has multiple beneficial properties. The use of Nigella sativa oil in association with a low or very low protein diet permits a decreased ingestion of nitrogen while avoiding the deleterious outcomes of inappropriate intake of dietary protein and malnourishment because it contains high amount of unsaturated fatty acids (Nickavar, Mojab, Javidnia, & Amoli, 2003). The antioxidant and anti-inflammatory activities of Nigella sativa are considered to be the key factors accountable for its nephroprotective effects (Salem 2005). Blood pressure lowering effect of Nigella sativa has been reported in previous studies (Dehkordi, & Kamkhah, 2008, Jaarin et al. 2015). In spite of association between Nigella sativa and its renoprotective activity, no clinical study done in hypertensive nephropathy. Therefore, aim of this study was to asses efficacy and safety of add-on therapy of Nigella sativa oil in hypertensive nephropathy.

Patients and methods

Patients. This study was conducted on patients of Chronic Kidney Disease due to hypertensive nephropathy in a tertiary healthcare centre of northern India attending Renal Clinic or admitted in IPD (In-Patient Department). This study was done in accordance with the declaration of Helsinki (1964) and its revised form (2008). Institutional Ethics Committee approved this prospective, randomized, parallel group and open label study, registered with Clinical Trials Registry-India (CTRI/2015/01/005371). Written and informed consent was given by each patient voluntarily. CKD due to hypertensive nephropathy was diagnosed on the basis of detailed medical history, examination and investigations.

Inclusion criteria. Stage 3 and 4 CKD patients due to hypertensive nephropathy and 20-60 years of age of either gender were included.

Exclusion criteria. Patients on dialysis, pregnant females, terminally sick and immuno-compromised or patients having severe renal disease, for example malignancy, were omitted from the study.

Study design. Total 65 patients were evaluated, in which 61 completed the study. 4 patients (2 of Group 1 and 2 of Group 2) were unsuccessful to complete the study. Random allocation software divided the patients randomly into two groups in a ratio of 1:1. After final diagnosis, applying inclusion and exclusion criteria, patients were enrolled in the study. Patients of Group 1 (Control) received conservative management (Telmisartan, Torsemide, Iron, Calcium, Vitamin D3, Erythropoietin) of hypertensive nephropathy while patients of Group 2 (Test) received conservative management along with Nigella sativa oil (2.5 mL, orally, once a day) (Figure 1). Treatment was continued for 12 weeks. Nigella sativa oil of 100% purity was used under the brand name "Kalonji oil" of Mohammedia Products, Hyderabad, India (GMP certified company).

Enrolled patients were regularly followed at 0, 6 and 12 weeks of treatment. Renal function test, blood pressure measurement, hemogram and serum electrolytes were estimated at each visit.

Safety Assessments

All adverse events were recorded on Adverse Drug Reaction (ADR) reporting form of Central Drugs Standard Control Organisation (CDSCO) at each visit. Causality and severity assessment were done by Naranjo Scale (Naranjo et al.,1981) and Modified Hartwig & Siegel

Scale (Hartwig, Siegel, & Schneider, 1992). respectively. A physical examination including evaluation of vital signs was done at the start of the study and on each visit. Additional routine laboratory tests like electrocardiogram (ECG), liver function test (LFT) and chest X-ray were performed in the beginning and at the end of the study.

Statistical analysis

The statistical data are expressed as mean ± SD (Standard Deviation). The comparison between pre and post treatment values in either group was done using Student's Paired T-test, while comparison between the groups was calculated with the help of Unpaired T-test. $P < 0.05$ was considered significant. SPSS (Statistical Package for the Social Sciences) software version 20 was used.

RESULTS

Group 1 included 32 patients (mean age 52.67 years) while Group 2 included 29 patients (mean age 50.07 years). Neither mortality nor anyone required dialysis in either group. According to GFR (mL/min/1.73 m^2) values, patients belonged to stage 3 (9 in Group 1 and 6 in Group 2) and stage 4 (23 patients in each group) CKD.

The initial signs and symptoms were: anorexia, nausea, vomiting, weakness, oliguria, weight loss, pruritus, edema, anemia and these were almost similar among the groups.

Various biochemical parameters and clinical features were improved gradually and progressively in both the hypertensive nephropathy groups but Nigella sativa oil treated group (Group 2) showed more improvement. There was significant ($p<0.001$) decrease in blood urea level in both the groups and group 2 also showed significant ($p<0.05$) change in comparison to group 1 at the end of study. Serum creatinine was reduced in both the groups but only group 2 showed significant ($p<0.001$) change in comparison to their initial value as well as to Group 1 at 12 weeks of study. Both diastolic and systolic blood pressures were decreased significantly ($p<0.001$) in both the groups but reduction was more marked in group 2 and it also showed significant change in systolic blood pressure in comparison to group 1 at the end of study. The total urinary protein (TUP) and total urinary volume (TUV) were improved significantly ($p<0.001$) in both the groups but it was more prominent and significant ($p<0.05$) in group 2 in comparison to group 1. GFR was improved in both the groups but group 2 showed significant change in comparison to group 1 as well as to their baseline value. Serum electrolytes were improved but within normal physiological range in both the groups (table 1).

Table 1: Effect of Nigella sativa oil on different parameters in hypertensive nephropathy patients. It shows different parameters of renal function test and serum electrolytes in Control (Group 1) and Test (Group 2) groups before and after 12 weeks of treatment.

S. No.	Parameters	Groups	At 0 week mean ± SD	At 12 weeks mean ± SD	% change after 12 weeks
1.	B. Urea (mg/dL)	1	68.17±20.02	61.10±20.92c	(−) 10.37%
		2	70.83±24.97	50.10±17.29c1	(−) 29.27%
2.	S. Cr. (mg/dL)	1	2.99±0.96	2.81±0.97	(−) 6.02%
		2	2.86±0.68	2.01±0.53c3	(−) 29.72%
3.	SBP (mm Hg)	1	157.00±9.03	141.00±5.80c	(−) 10.19%
		2	157.53±17.85	132.67±18.79c1	(−) 15.78%
4.	DBP (mm Hg)	1	93.60±7.94	84.47±4.09c	(−) 9.75%
		2	94.53±14.14	83.20±4.25c	(−) 12.00%
5.	TUV (mL/day)	1	1768.33±240.14	2025.00±194.65c	(+) 14.51%
		2	1743.33±345.85	2141.67±248.47c1	(+) 22.85%
6.	TUP (g/day)	1	1.39±0.87	1.04±0.75c	(−) 25.18%
		2	1.18±0.81	0.65±0.46c1	(−) 44.91%
7.	GFR (mL/min)	1	23.46±8.72	27.17±13.87	(+) 15.81%
		2	23.22±6.83	35.22±10.99c1	(+) 51.68%
8.	Na+ (mEq/L)	1	134.40±3.01	135.10±2.87	(+) 0.52%
		2	137.40±3.16	140.93±6.14b3	(+) 2.57%
9.	Ca2+ (mg/dL)	1	8.47±1.47	9.18±0.22a	(+) 8.38%
		2	8.73±0.20	9.49±0.21c	(+) 8.71%
10.	K+ (mEq/L)	1	4.32±0.36	4.16±0.39	(−) 3.70%
		2	4.37±0.36	4.04±0.23c	(−) 7.55%

Values are mean ± SD; $p<0.05$ was considered significant; [a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$ compared to 0-week value of respective group; [1]$p<0.05$, [2]$p<0.01$, [3]$p<0.001$ compared to control group. 1=Control Group; 2=Test Group; B. Urea= Blood Urea; S.Cr.= Serum creatinine; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; TUP= 24-Hour Total Urinary Protein; TUV= 24-Hour Total Urinary Volume; GFR= Glomerular Filtration Rate; Na^+= Serum Sodium; Ca^{2+}= Serum calcium; K^+= Serum potassium; (-) decrease; (+) increase.

According to Modified Hartwig & Siegel Scale, the adverse drug reactions were mild (no hospitalization, no change of therapy and no additional treatment) in test group. No adverse event was of acute onset (within 60 minutes). The ADRs were possible (Score = 1-4) in 2 cases and probable (Score = 5-8) in 1 case with Group 2 (table 2) on the basis of Naranjo's Scale.

Table 2: Shows adverse drug reactions (ADRs) in test group

S. No.	ADRs Recorded	Group 2 (n=29)
1.	Nausea	1
2.	Diarrhea	1
3.	Rashes	1
4.	Altered taste	1

DISCUSSION

Conservative management has crucial role to obviate CKD and to prevent its progression towards End Stage Renal Disease (ESRD). It offers only symptomatic relief and delays the progressive deterioration of renal functions in hypertensive nephropathy. So, innovative treatment modalities are being explored which can halt injury to nephron, delay the progress of ESRD from hypertensive nephropathy and cost effective. Renal Replacement Therapy (RRT) is the ideal treatment modality for CKD-ESRD. In India, more than 1 lakh new patients enter RRT per annum (Kher 2002). Only 10% of Indian patients with ESRD receive any form of RRT due to inadequate resources and high cost. Present study revealed that Nigella sativa oil improved the blood pressure control and enhanced kidney functions in patients of hypertensive nephropathy. It has blood pressure lowering property established by previous studies (Dehkordi, & Kamkhah, 2008, Jaarin et al., 2015). Although we did not measure indices of antioxidant defense system and lipid peroxidation, our assumption is that the reduction in blood pressure was in part due to antioxidant activity of Nigella sativa oil. Essential oil of Nigella sativa seed has antioxidant property that makes it useful for treating cardiovascular disorders (Burits, & Bucar 2000). Add-on therapy of Nigella sativa oil improves renal function in stage 3 and 4 CKD patients. (Ansari, Nasiruddin, Khan, & Haque, 2016). Blood pressure, blood sugar, total cholesterol and triglyceride levels were decreased. So, it might be useful in CKD due to prolonged and uncontrolled hypertension and diabetes (Shah et al., 2012). Thymoquinone is the principal constituent of Nigella sativa oil which reduces various inflammatory markers and has strong antioxidant property (Meziti, Meziti, Boudiaf,, Budancamanak, & Demirel, 2012) The potent antioxidant and anti-inflammatory properties of Nigella sativa are considered the key factors accountable for its nephroprotective effect. Due to strong antioxidant, anti-inflammatory, nephroprotective, antihypertensive activity, Nigella sativa oil can be used as a natural adjuvant in the treatment of hypertensive nephropathy.

Nigella sativa oil (2.5 mL, p.o., once daily) showed beneficial effects in stage 3 and 4 of CKD due to hypertensive nephropathy. None of the previous clinical studies have reported any untoward or serious

adverse side effects of Nigella sativa. The results in our study are in congruence with those reported previously. The cardiovascular protective role of Nigella sativa in hypertension are probably added by its multitude actions including cardiac depressant, diuretic, calcium channel blockade and antioxidant properties. It has been used as a traditional medicine for the treatment of hypertension for many years. Hence, add-on therapy of Nigella sativa oil produces improvement in biochemical parameters and clinical features and safe in patients of hypertensive nephropathy. Thus, we suggest that molecular level studies are needed to confirm its broad-spectrum effects not only on hypertensive nephropathy but on various diseases in which Nigella sativa is traditionally used as palliative to cure these diseases.

CONCLUSION

Nigella sativa oil has the potential to be used as a natural adjuvant to conservative treatment in the management of hypertensive nephropathy and it is a very low-cost medicinal herb. Therefore, add-on therapy of Nigella sativa oil boosted the therapeutic advantage of conservative management in patients of hypertensive nephropathy.

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Conflict of interests

Authors have no conflict of interests.

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