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ROLE OF NIGELLA SATIVA IN RENOPROTECTION

Pharma

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ABSTRACT

Objective: To evaluate the role of Nigella sativa in renoprotection

Material and Methods: This prospective, comparative study was completed in a tertiary care centre of north India in patients of Chronic Kidney Disease (CKD). Group I (Control) received conservative management of CKD and while Group II (Test) received conservative management along with Nigella sativa oil (2.5 mL, orally, once daily) for 12 weeks. Renal function tests were done at 0, 6 and 12 weeks of treatment.

Results: There was more progressive improvement in biochemical values and clinical signs and symptoms in test group. There was decrement in blood urea, serum creatinine and 24-hour total urine protein (TUP). There was rise in glomerular filtration rate (GFR) and 24-hour total urine volume (TUV).

Conclusion: Nigella sativa oil supplementation is effective and safe in prevention of progression of nephropathy.

KEYWORDS

Renoprotection, Nigella sativa oil, GFR.

INTRODUCTION

Chronic Kidney Disease (CKD) is defined as: kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 months or more, regardless of cause (National Kidney Foundation, 2002). CKDs are developing as a universal threat to human health. And its prevalence was approximately 17.2% (Singh et al., 2013). Dialysis or kidney transplantation prolongs survival in patients with end-stage renal disease (ESRD) but the provision of adequate treatment to all is absorbing a large proportion of the health care budget, so clinicians should be looking for ways to prevent the need for dialysis in as many patients as possible. Simple and low-cost treatments in the form of supplementation therapy are conceivable and possibly effective. In India, nearly 1 lakh new patients of ESRD require renal replacement therapy annually (Sakhuja & Sud, 2003). Ingestion of low protein diet (0.6 g/kg BW/day) and very low protein diet (0.3 g/kg BW/day) can reduce metabolic nitrogenous waste products in the body while keeping an acceptable nutritional status. So, secondary problems such as proteinuria, deterioration of renal function, bone disease and metabolic acidosis are reduced (Chang et al., 2009, Fouque, Laville, & Boissel, 2006).

Research by El-Shamy, Mosa, El-Nabarawy and El- Qattan (2011) support renoprotective property of Nigella sativa in diabetic patients. A randomized clinical trial established that Nigella sativa oil improved renal function as well as liver function. In addition, it also has anti-inflammatory properties (Mohtashami et al., 2011), which is good for nephroprotection.

Fixed and essential oils are important constituents of Nigella sativa oil. Thymoquinone, cymene and carvone are foremost important components of essential oil while fixed oil contains mainly linoleic acid, oleic acid, palmitic acid and stearic acid. Thymoquinone is the key active component of Nigella sativa oil which has several beneficial and clinically effective properties. Low or very low protein diet along with Nigella sativa oil supplementation in patients of chronic kidney disease allows a diminished intake of nitrogen while evading the harmful consequences of unsuitable intake of dietary protein and malnourishment because it contains high amount of unsaturated fatty acids which also provide nutrition along with essential nutrients (Nickavar, Mojab, Javidnia, & Amoli, 2003). Nigella sativa has strong antioxidant as well as anti-inflammatory properties which are considered the key accountable factors responsible for its renoprotective activites (Salem, 2005). Inspite of theoretical association between Nigella sativa oil and its role as renoprotectant, there is no clinical study reported previously to assess its protective role in patients of chronic kidney disease due to various etiologies. Hence the aim of our study was to assess the effectiveness as well as safety of Nigella sativa oil supplementation in patients of Chronic Kidney Disease.

MATERIAL AND METHODS

Patients. This study was conducted & completed in the patients diagnosed with Chronic Kidney Disease due to various etiologies in a medical college and hospital of northern India. This clinical study was carried out in accordance with the declaration of Helsinki (1964) as well as its revised form (2008). Institutional Ethics Committee approved this open label, prospective, randomized and parallel group study in patients of CKD. This research work is listed with registration number CTRI/2015/01/005371 in Clinical Trials Registry-India (CTRI). Written and informed consent were given by all the patients enrolled in the study voluntarily before start of the research work. The diagnosis of CKD was made and confirmed on the basis of detailed medical history, physical examination, investigations (renal function tests) and other biochemical parameters.

Inclusion criteria.

Patients diagnosed with CKD stage 3 and stage 4 and age group 20-60 years of either sex were included in the study.

Exclusion criteria.

Pregnant women, patients on dialysis, terminally and critically sick, immuno-compromised patients or patients with severe renal pathology such as malignancy.

Sample size (n).

p=prevalence (prevalence assumed as17.2% according to SEEK-India cohort study, 2003); q=1-p. Hence, sample size (n) = [(1.96*1.96)/(0.09*0.09)]* [0.172*0.828]=67.54. So, sample size consists of 68 patients is minimum requirement for each group but we recruited more than 68 patients in each group because of dropout rate.

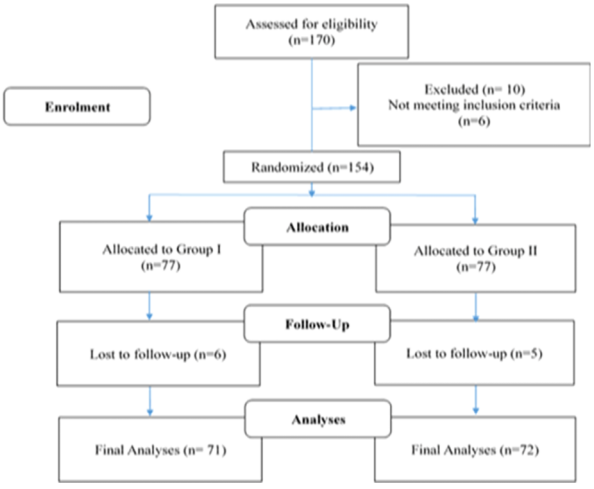
Study design.

Ultimately 154 patients were recruited and registered in the study after evaluating total 170 patients. On successive visits, 11 patients (6 of Group I and 5 of Group II) failed to report, so they were excluded from the study. All the registered patients of CKD were randomized into two groups in a ratio of 1:1 with the help of random allocation software. Each block of randomization table had 20 subjects to lessen the discrepancy and inconsistency between the two groups at any time of study period with respect to number of patients. After application of inclusion and exclusion criteria as well as final diagnosis, patients were finally contained in the study. received Conservative management of CKD (Telmisartan, Torsemide, Iron, Calcium, Vitamin D3, Erythropoietin, Insulin in case of diabetic patients) was given in

patients of Group I (Control) while Group II (Test) patients received conservative management of CKD along with Nigella sativa oil (2.5 mL, per orally, once daily,) (Figure 1). Treatment was given for 12 weeks in both the groups. 100% pure Nigella sativa oil was used for this study and it was commercially available and purchased from local market under brand name "Kalonji oil" from Mohammedia Products, Hyderabad, India (a GMP certified company).

All the patients enrolled in the study were regularly followed with renal functions tests and serum electrolytes at 0, 6- and 12-weeks interval of treatment.

Fig.1: Shows recruitment, allocation and follow-up of participants



Safety Assessments

All adverse events or reactions experienced and/or noticed by patient or detected by the investigator were recorded on standard Adverse Drug Reaction (ADR) reporting form of Central Drugs Standard Control Organisation (CDSCO) at each visit. Naranjo Scale (1981) was used for causality assessment while severity assessment was done with the help of Modified Hartwig & Siegel Scale (Hartwig, Siegel, & Schneider, 1992). Physical examination and inspection that also included assessment of vital signs of the patients was done at the start of study and on each succeeding visit. Supplementary routine laboratory safety tests like ECG, X-ray of chest and liver function test (LFT) etc. were performed whenever required. All the ADRs were informed and reported to the ADR monitoring centre (AMC) of the medical college and hospital.

Statistical analysis

The values were expressed as mean ± SD. In each group, statistical significance between pre and post treatment values was calculated using Student's Paired T-test, while Unpaired T-test was used to calculate statistical significance between the groups was calculated with the help. The value $P < 0.05$ was considered significant. Statistical analysis was done using SPSS-20 software.

RESULTS

71 patients (42 Male, 29 Female) were included in Group I and their mean age was 44 years (range 20-60 years) while Group II included 72 patients (36 Male, 36 Female) and mean age was 45 years (range 20-60 years). The distribution of patients was almost similar among the groups. There was neither mortality nor anyone required dialysis in either group. According to GFR (mL/min/1.73m^2), patients belonged to stage 3 (16 in Group I and 11 in Group II) and stage 4 (55 and 61 in Group I and II respectively) of CKD in both the groups. The prominent causes of CKD were: diabetic nephropathy (15.49% and 31.94%), hypertensive nephropathy (45.07% and 40.28%), chronic glomerulonephritis (11.26% and 8.33%), tubulointerstitial nephritis (5.63% and 6.94%), Autosomal Dominant Polycystic Kidney Disease (2.82% and 2.78%) and unknown causes (19.72% and 9.72%) in group I and group II respectively.

The signs and symptoms- anorexia, nausea, vomiting, headache, pruritus, weakness, weight loss, edema over the body, anemia, oliguria, hypertension etc. were found in the patients at the start of the therapy. The clinical features were almost similar among the groups at 0 week of the study. The various clinical features and biochemical parameters were improved gradually and progressively in both the groups after 12 weeks of treatment but it was more noticeable in group II (Nigella sativa oil supplemented group).

Serum creatinine was significantly decrease in Group I ($p<0.05$) and Group II ($p<0.001$) in comparison to their initial values and Group II also showed a significant change ($p<0.001$) in serum creatinine compare to Group I at the end of study. Both the groups showed significant change in blood urea ($p<0.001$) but statistically significant change ($p<0.001$) in blood urea level was also observed in Group II in comparison to Group I after 12 weeks of treatment. GFR was significantly increased in both groups while Group II also showed significant change ($p<0.001$) in comparison to Group I at 12 weeks. There was significant decrease in TUP ($p<0.001$) in both the groups and Group II also showed statistically significant change ($p<0.001$) compared to Group I after 12 weeks. There was significant increase in TUV ($p<0.001$) and Group II also showed a significant reduction ($p<0.01$) compare to Group I at 12 weeks.

Table 1: Shows renal function tests and serum electrolytes in Control (Group I) and Test group (Group II) before and after 12 weeks of treatment.

Sr. No.	Parameters	Groups	At 0 week Mean ± SD	At 12 weeks Mean ± SD	% change after 12
1.	S. Cr. (mg/dL)	I	2.92±0.82	2.75±0.90^a	(−) 5.82%
		II	2.93±0.86	2.00±0.59^{c3}	(−) 31.74%
2.	B. Urea (mg/dL)	I	70.32±21.74	62.87±20.36^c	(−) 10.60%
		II	71.85±22.20	50.43±26.89^{c3}	(−) 29.81%
3.	GFR (mL/min)	I	25.07±9.30	28.40±12.35^b	(+) 13.30%
		II	23.42±7.32	36.64±11.77^{c3}	(+) 56.45%
4.	TUV (mL/day)	I	1737.32±326.53	1982.40±311.34^c	(+) 14.11%
		II	1693.75±336.40	2111.11±278.10^{c2}	(+) 24.64%
5.	TUP (g/day)	I	1.40±0.99	1.01±0.72^c	(−) 27.86%
		II	1.20±0.82	0.66±0.51^{c3}	(−) 45.00%
6.	K^+ (mEq/L)	I	4.34±0.42	4.23±0.42^a	(−) 2.54%
		II	4.38±0.40	4.04±0.23^{c2}	(−) 7.76%
7.	Na^+ (mEq/L)	I	134.92±10.46	135.55±3.22	(+) 0.47%
		II	136.53±3.09	139.61±6.24^{c3}	(+) 2.25%

Values are mean ± SD; $p<0.05$ was considered significant; $^ap<0.05$, $^bp<0.01$, $^cp<0.001$ compared to 0-week value of respective group; $^1p<0.05$, $^2p<0.01$, $^3p<0.001$ compared to control group. I=Control; II=Test; S. Cr.= Serum creatinine; B. Urea= Blood Urea; GFR = Glomerular Filtration Rate; TUV= 24 Hour Total Urinary Volume; TUP= 24 Hour Total Urinary Protein; K^+= Serum potassium; Na^+= Serum Sodium; (-) decrease; (+) increase.

According to Modified Hartwig & Siegel Scale, 1992, the observed and recorded adverse drug reactions were mild (there were no change of therapy, no additional treatment and no hospitalization) in severity in test group. No adverse event was recorded of acute onset (within 60 minutes). On Naranjo's Scale (1981) the ADRs were possible (Score = 1-4) in 6 cases and probable (Score = 5-8) in 2 cases with Group II (table 2).

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

Sr. No.	ADRs Recorded	Group II (n=72)
1.	Nausea	2
2.	Diarrhea	2
3.	Vomiting	1
4.	Altered taste	2

5.	Excessive thirst	1
6.	Rashes	1

DISCUSSION

To alleviate the clinical signs and symptoms of CKD and to avert advancement of it to end stage renal disease (ESRD), conservative management is very imperative in treatment. It postpones the progressive deterioration of functioning of kidney and offers only symptomatic relief. So, novel, clinically beneficial and cost-effective modalities of treatment are being explored which can halt progressive injury to nephron and delay the development of ESRD. Due to rapid upsurge in the prevalence of diabetes and hypertension globally, CKD has appeared as a leading chronic disease worldwide (Wild, Roglic, Green, Sicree, & King, 2004, Gupta, 2004). Premature morbidity and mortality have arisen due to various nephropathy and it hampers quality of life. In India, CKD is a major public health problem now a days for both health sector and economy. Renal Replacement Therapy (RRT) is the ideal treatment for CKD-ESRD which consists in the form of renal transplantation and maintenance dialysis. According to Kher (2002) more than 100,000 new patients enter RRT annually in India. Only 10% of ESRD patients in India receive any form of RRT due to inadequate resources and high cost of therapy. The cost of Continuous Abdominal Peritoneal Dialysis (CAPD) is $600 whereas hemodialysis costs $300 per month. The cost of kidney transplant is $8900 in the first year, which decreases later to $3000 per annum. Renal transplant is the preferred and ideal choice and offers improved quality of life but still only a little fraction of Indians can afford it (Kher, 2002).

Systemic inflammation and raised inflammatory markers are characteristic features of CKD and cardiovascular diseases. Yusof, Ling, Muhamad and Suhaimin (2012) proved by their research that mixture of Nigella sativa with honey reduced the levels of inflammatory markers as well as improved lipid profile. In another study it was reported that Nigella sativa seeds supplementation was useful in metabolic syndrome. Blood pressure, blood sugar, total cholesterol and triglyceride levels were decreased. So, it might be useful in CKD due to diabetic and hypertensive nephropathy (Shah et al., 2012). Dehkordi and Kamkhah (2008) have reported the antihypertensive activity of Nigella sativa., so it might be useful in CKD due to prolonged and uncontrolled hypertension. Thymoquinone is the principal and clinically effective active constituent of Nigella sativa oil which reduces the serum levels of inflammatory markers like IL-1 and TNF-α (Tekeoglu, Dogan, Ediz, Budancamanak, & Demirel, 2007). The antioxidant and anti-inflammatory activities of Nigella sativa are considered the key factors accountable for its nephroprotective avtivity (Salem, 2005). Administration of Nigella sativa extract with injection of gentamycin led to increased Superoxide dismutase (SOD) and Glutathione peroxidase (GSHPx) activities and statistically significant reduction in blood urea, serum creatinine, malondialdehyde (MDA) and Nitric oxide (NO) generation when compared with gentamicin group in rats (Bayrak et al., 2008). Due to its strong antioxidant, antidiabetic, antihypertensive, anti-inflammatory, nephroprotective and hypolipidemic properties, Nigella sativa oil can be used in CKD due to various etiologies for its nephroprotective role.

Nigella sativa oil at dose of 2.5 mL (orally, once daily) showed beneficial effects in CKD stage 3 and stage 4 patients. No earlier clinical studies have stated the serious and untoward adverse effects of Nigella sativa. Thus, the adverse events might be the indexes of underlying renal pathology or due to some other co-administered medications.

The results of our study are in resemblance with those reported in previous studies. Hence, conservative management of chronic kidney disease along with Nigella sativa oil supplementation produces improvement in biochemical parameters as well as clinical features and safe in various nephropathies. Further studies will help to better recognize the renoptotective role of Nigella sativa in improving renal functions. Thus, we suggest that molecular level studies are needed to confirm its broad-spectrum effects not only on CKD but on various diseases in which Nigella sativa is traditionally used as palliative to cure these diseases.

CONCLUSION

Nigella sativa oil supplementation improved the therapeutic benefit of conservative management in stage 3 and stage 4 patients of Chronic Kidney Disease.

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Conflict of Interests

Authors have no conflict of interests.

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