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BRIEF REPORT

Arpana Iyengar · Hrishikesh Damle · Chanda Kulkarni · Latha Damle · Kishore Phadke

Steroid sparing effect of a herbal preparation in steroid-dependent nephrotic syndrome

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Abstract Investigations on plants are revealing the potential therapeutic benefits of medicinal herbs in treating immunological disorders. Nephrotic syndrome has emerged as an immunological disorder. Steroid dependence poses a therapeutic challenge in the management of nephrotic syndrome. Our pilot study compares the efficacy of an ayurvedic polyherbal preparation 'Shathavaryadi Yoga (NS001)' with oral cyclophosphamide in maintaining remission in steroid-dependent nephrotic syndrome.

Keywords Cyclophosphamide · Cyclosporine · Herbal medicines

Introduction

The long-term administration of steroids to children with steroid-dependent nephrotic syndrome (SDNS) entails the risk of serious side effects. Although many immunosuppressants, such as cyclophosphamide and cyclosporine, have been used in these situations, with varying success [1–3], there are definite limitations to their efficacy not to mention their toxicity and cost [4]. Consequently, there is a need to explore other safer and efficacious options for treating children with SDNS. In traditional Chinese medicinal practice, herbal extracts are extensively used in treating nephrotic syndrome [5].

Ayurvedic medicine is a formulary of herbal extracts forming a traditional knowledge system of medicine native to India and recognized in the Drugs and Cosmetics Act Of India, 1942. A polyherbal preparation called 'Shathavaryadi Yoga (NS001)' was identified for our study. This polyherbal preparation consists of multiple ingredients in varying proportions: *Asparagus racemosa* (12.4%), *Pueraria tuberose* (12.4%), *Diascorea bulbifera* (15.5%), *Tinospora cordifolia* (19.37%), *Semecarpus anacardium* (1.55%), *Plumbago zeylanica* (7.75%), *Sesamum indica* (12.4%), *Tribulus terrestris* (12.4%) and a mixture of trikatu containing *Piper longum*, *P. nigrum* and *Zingiber officihnalis* (6.2%). These ingredients are known to have immunomodulatory, antioxidant, anti-inflammatory and hypolipidemic properties and have been used to treat edematous states in Ayurvedic medicine, including nephrotic syndrome [6].

The present pilot study was designed to evaluate the safety and efficacy of the polyherbal preparation NS001 in treating children with SDNS.

Materials and methods

This pilot study was designed as a randomized controlled open trial to evaluate the efficacy and safety of NS001 in maintaining remission in children with SDNS as compared to conventional oral cyclophosphamide therapy. In accordance with the International Study of Kidney Diseases in Children (ISKDC), a relapse was considered to have occurred when the urine protein creatinine ratio was >2 and/or 24-h urine protein was >1 gm/m^2 per day [7]. Newly diagnosed children with SDNS in the age group 1–12 years were included in the study. Exclusion criteria were the presence of atypical features or renal dysfunction. These children were treated with 2 mg/kg per day of steroids for 2 weeks or longer until they went into remission when they were switched over to 1.5 mg/kg per alternate day of

A. Iyengar · K. Phadke (✉)
Childrens' Kidney Care Center,
Department of Paediatrics,
St Johns Medical College Hospital,
Bangalore, 560034, India
e-mail: kishorephadke@vsnl.com
Tel.: +91-80-22065284
Fax: +91-80-25530070

C. Kulkarni
St Johns Medical College,
Bangalore, 560034, India

H. Damle · L. Damle
ATRIMED Pharma,
No. 15, 16, 6th floor,
Vayudoot Chambers,
Trinity Circle, M. G Road,
Bangalore, India

steroids. This switch-over day was considered to be day zero of the study. Ethical clearance was obtained from the Institutional Review Board of the hospital. An informed consent was obtained from the parents prior to enrollment of the children into the study. The herbal preparation was screened for steroids by thin layer chromatography, for heavy metal content by atomic absorption spectrophotometry and for microbial contamination by an Indian standard specification method. The study population (20 patients) was randomly allocated to two groups using the random number table. On day zero, Group 1 children received NS001 orally in the dosage of 45 mg extract/kg per day (5 ml = 500 mg of extract); the same dose was continued until day 180. Group 2 children received cyclophosphamide in dosages of 2–3 mg/kg per day for 60 days, with the maximum cumulative dose being <168 mg/kg. Both groups received steroids in the dosage of 1.5 mg/kg per alternate day for 4 weeks, after which time the dosage was tapered off over the next 4 weeks and eventually discontinued after 8 weeks. The time of occurrence of a relapse – if any – was noted. The occurrence of a relapse while off medications was taken as a measure of therapeutic efficacy.

The drug (NS001 or cyclophosphamide) was discontinued in children who had adverse drug reactions, if there was non-compliance of the drug for >7 days or if there was a relapse. The patients were followed up at 2-week intervals for first 2 months, monthly for next 5 months and thereafter every 3 months for 1 year. Spot urine protein: creatinine ratios, 24h urine protein estimation, serum albumin and serum cholesterol were tested serially, and a urine dipstick examination for protein was conducted daily in the home setting. Safety was assessed on the basis of the medical history, by a physical examination at each visit and with serial blood tests (blood counts, renal function tests, liver function tests). Statistical analysis was conducted using Fischer's test with the SPSS 10.00 package (SPSS Inc., Chicago, Ill.).

Results

The male:female ratio was 7:3 in Group 1 (receiving NS001) and 6:4 in Group 2 (receiving cyclophosphamide). The mean age of Group 1 was 47.9 months (95% CI: 29.56–66.24) and of Group 2, 84.9 months (95% CI: 62.28–107.52). The mean duration of nephrotic syndrome from the time of initial episode was 20.24 months (95% CI: 7.07–33.4) in Group 1 and 26.28 months (95% CI: 8.73–43.84) in Group 2. The mean body weight was 15.86 kg (95% CI: 12.07–19.65) and 16.18 kg (95% CI: 12.71–19.65) in Group 1 and 2, respectively.

Seven out of ten children in Group 1 had a relapse within 6 months and eight relapsed within 12 months of discontinuing NS001. Five out of ten children from Group 2 had a relapse within 6 months and six children relapsed within 12 months following discontinuation of cyclophosphamide. The difference in the relapse rates was not statistically significant ($p>0.05$ by Fischer's test). In our study the 'drug-free interval' was considered to be the time from discontinuation of the respective drug in both groups to the occurrence of the first relapse, and was taken to be a measure of therapeutic efficacy. The mean drug-free intervals for the children of Group 1 and Group 2 were 6.7 months and 8.6 months, respectively. The difference in the drug-free intervals between the two groups was not significant ($p>0.5$).

Adverse events

One child from Group 1 developed microscopic hematuria 6 weeks after the drug treatment had been initiated; this condition resolved 3 weeks after the medication was stopped. Another child in the same group developed viral hepatitis (HAV IgM positive) 1 month after completing the NS001 therapy; complete recovery occurred within 4 weeks. A child from Group 2 had leucopenia (total count: 2,600/cmm) on day 45 of post-initiation of the cyclophosphamide treatment. With discontinuation of the drug for 2 weeks the counts reverted to normal. Cyclophosphamide was restarted at a lower dosage to complete the course without any adverse effects.

Discussion

This pilot study compares the efficacy of an ayurvedic medication with that of cyclophosphamide in children with steroid-dependent nephrotic syndrome. Renal biopsy was not carried out on any of the children in either group. Although the duration of treatment in the two groups was different, the schedule for tapering and discontinuation of steroids was similar in both groups. One limitation to the study is that although Group 1 and 2 were randomized, the participants in the groups were not matched for age and weight. The rationale in using herbal medications in this study was based on the immunological pathogenesis of nephrotic syndrome. During a relapse the T suppressor lymphocyte cell activity increases and the interleukin-2 (IL-2) levels as well as those of tumour necrosis factor-alpha (TNFα) and other permeability factors levels are high [8]. Decreased antioxidant defense and an increase in apoptosis rate contribute to the functional abnormalities of T cells in nephrotic syndrome [9]. The major constituent of the herbal preparation is *Tinospora cordifolia* (Amrutha in Sanskrit). The active ingredients of *Tinospora* are various alkaloids and glycosides (TC1–7), which have immunostimulating and immunomodulatory properties, such as the augmentation of IgG antibodies and the inhibition of IL-1 and TNF-alpha production by macrophages. Therapeutic doses of *Tinospora* have been shown to reduce apoptosis [10]. Apart from the immunomodulatory properties, *Tinospora* has also been proven to have an antioxidant and anti-inflammatory effect. The herb has been used to treat anasarca [11].

Piper longum has been shown to have an anti-inflammatory activity. *Diascorea bulbifera* is a strong diuretic, and *Piper nigrum* is a weak diuretic with anti-edema

properties. *Zingiber officinale*, whose active principle is gingerols, has been reported to inhibit prostaglandin synthesis, which contributes to anti-inflammatory and anti-platelet activity [12].

One child from Group 2 had leucopenia which was transient. The reported incidence with cyclophosphamide causing leucopenia is 15% [5]. The appearance of microscopic hematuria has not been documented to date in the literature on ayurvedic medicine as a known side effect of any of the herbal drugs used in this study.

Conclusion

Shathavaryadi yoga (NS001) was found to be as effective as cyclophosphamide in sustaining remission in steroid-dependent nephrotic syndrome. While cyclophosphamide has a serious limitation of cumulative toxicity, NS001 may have an advantage in long-term use as a steroid-sparing agent. Further studies with a longer duration of therapy and a larger study sample are recommended.

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