Intravenous Pulsed Cyclophophamide versus Intrvenous Vincristine Therapy in Steroid Dependent Nephrotic Syndrome: A Randomised Controlled Trial

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Abstract - Objective - Childhood nephrotic syndrome (NS) is characterised by a relapsing course resulting in a significant corticosteroid burden or prescription of cytotoxic immunosuppressive therapy. This randomised controlled study was carried out over a peroid of 3 years at a single centre in Sri Lanka to compare the efficacy and safety of intravenous cyclophosphamide (CYC) or intravenous vincristine in treating children with steroid dependent NS.

Methods - Thirty nine sequential children with steroid dependent NS with evidence of steroid toxicity were randomly allocated to receive either intravenous cyclophosphamide (500 mg/m^2 monthly for 6 months) or vincristine (1.5mg/ m^2 weekly for 4 weeks followed by 4 doses monthly). Both groups received an identical tapering regimen of oral prednisolone for 6 months. All children were reviewed on monthly basis for one year focusing on recurrence of proteinuria and adverse effects of therapy. Presence of 3+ proteinuria for 3 consecutive days was considered as a relapse.

Results - There were 18 children in the cyclophosphamide group (mean age 6.4 years) and 21 in the vincristine group (mean age 7.2 years). During one year of follow up 6/18 (33.3%) in the cyclophosphamide group suffered a relapse while 13/21 (61.9%) suffered a relapse in the vincristine group with $p < 0.05$ (comparison of 2 proportions using Standard Error. CI 0.105 to 0.49). No serious adverse effects were encountered in either group.

Conclusion - In steroid dependent NS, intravenous cyclophosphamide therapy is superior to intravenous vincristine therapy in maintaining sustained remission.

Keywords: Steroid-dependent nephrotic syndrome, intravenous, cyclophosphamide, vincristine, relapse, remission

I. INTRODUCTION

Nephrotic syndrome (NS), described by the triad of generalised oedema, heavy proteinuria and hypoalbuminaemia, is the commonest glomerular disease in children. It has an annual incidence of 2-7 per 100,000 children1. International Study for Kidney Diseases in Children (ISKDC) defines steroid dependent nephrotic syndrome (SDNS) as children in whom two consecutive relapses whilst receiving corticosteroid therapy or within 14 days of discontinuing steroid therapy2.

As frequent relapses and steroid dependency results in repeated courses of corticosteroids, the risk of corticosteroid related side effects such as suppression of hypothalamus-pituitary-adrenal axis, growth retardation, hypertension, bone disease and cushinoid features is high[3]. Therefore steroid-sparing agents are introduced in order to minimise unacceptable side effects. Although many drugs were used as potential steroid-sparing agents, immunmodulating agents (levamisole), mycophenolate mofetil, alkylating agents (cyclophosphamide, chlorambucil) and calcineurin inhibitors (cyclosporine) are the only ones proven to maintain stable remission in FRNS and SDNS by randomised controlled trials[4].

Cyclophosphamide is a well established-steroid sparing drug used in NS, whereas vincristine is a chemotherapeutic agent which has gained attention as a potential adjuvant therapy in NS. The present study assesses and compares the efficacy of intravenous cyclophosphamide and vincristine in maintaining remission in SDNS.

II. PATIENTS AND METHODS

This randomized, single-centre study was conducted at the Professorial Paediatric Unit, Teaching Hospital Peradeniya, Sri Lanka from 2004-2007. Thirty-nine sequential children with SDNS showing evidence of steroid toxicity relapsing while receiving over 30mg/m^2 of prednisolone were randomly allocated for either a course of intravenous cyclophosphamide or vincritine. The cyclophosphamide regimen consisted of 500 mg/m^2 doses infused monthly for a period of 6 months. Vincristine was infused as 1.5mg/m^2/week for 4 weeks, followed by 1.5mg/m^2/month for 4 months.

An identical tapering regimen of oral prednisolone was given to both groups during this time. This regimen consisted of 30 mg/m^2 prednisolone on alternate-days for 1 month, which was tapered by 5mg/m^2 every 4 weeks over a period of 6 months. All patients were reviewed on a monthly basis for a period of one year, focusing mainly on recurrence of proteinuria and any side effects. All parents were trained to test early morning samples of urine for protein and record it daily in the patient-held record book. Urine protein excretion of 3+ or more for 3 consecutive days was considered as a relapse.

Patients who had a renal histology other than minimal change disease (MCN), patients who had nephrotic syndrome due secondary causes and previously had other immune suppressive therapy such as cyclosporine A or mycofenalate mofetil were not recruited into this study.

III. RESULTS

A group of 18 children received intravenous cyclophosphamide, in which 11 were male and 7 were female. Their mean age was 6.4 years. Twenty-one children with a mean age of 7.2 years received vincristine therapy. In this group 15 were males and 6 were females.

During the one-year follow up 6 (33%) patients on cyclophosphamide suffered a relapse, while 13 (62%) patients relapsed in the vincristine group. In the vincristine group this percentage was significantly higher with a p value of 0.03 (comparison of 2 proportions using Standard Error. CI 0.105 to 0.49). No serious side-effects were observed in either group. The results are summarised in table 1 and figure 1.

Table 1. SUMMARY OF RESULTS

	Intravenous CYC therapy	**Intravenous Vincristine therapy**
Total number of patients who received the therapy Males Females	18 11 07	21 15 06
Dose	500 mg/m^2 monthly for 6 months	4 doses of 1.5mg/ m^2 weekly, followed by 4 doses monthly
Duration	6 months	5 months
Mean age (years)	6.4	7.2
Number of patients who relapsed at 1 year of follow-up	6/18 (33.3%)	13/21 (61.9%)
Sustained remission at 1 year	12/18 (66.7%)	8/21 (38.1%)

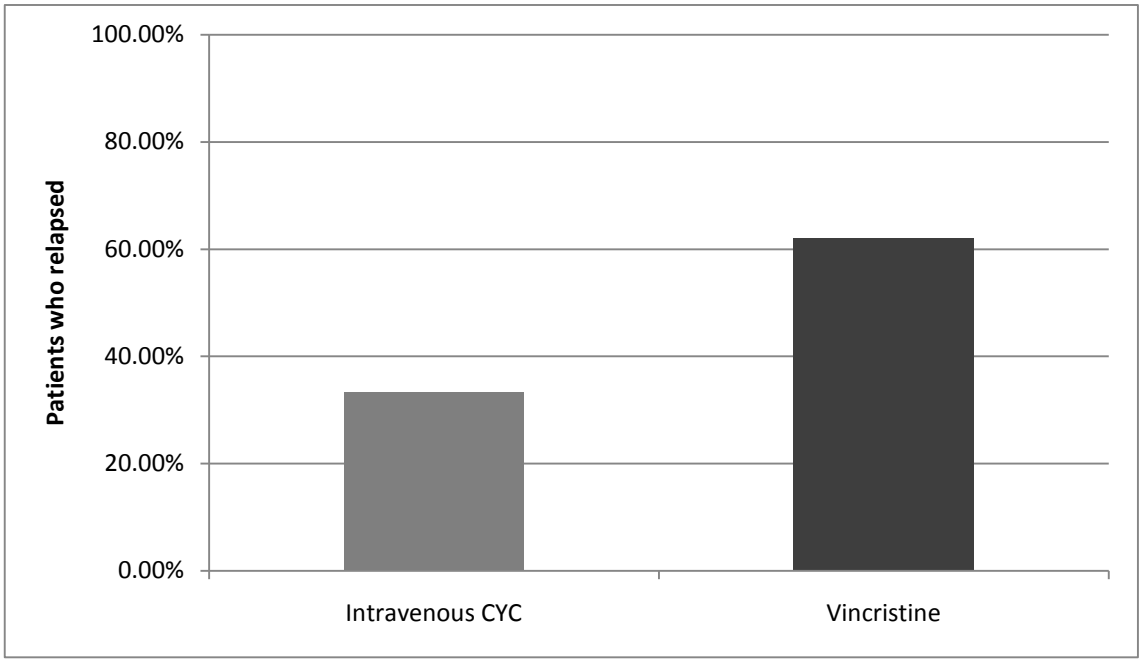

Figure 1. Percentages of patients in the two groups who relapsed

V. CONCLUSION

From the results of this study we conclude that intravenous cyclophosphamide therapy is superior to intravenous vincristine in maintaining sustained remission in SDNS.

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