International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

CYCLOPHOSPHAMIDE IN CHILDREN WITH IDIOPATHIC NEPHROTIC SYNDROME

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ABSTRACT

Treatment of Idiopathic nephritic syndrome with steroid dependent or frequent relapse is controversial. Many immunosuppressive drugs have been proposed. This is a review to help in choosing first line treatment with steroid dependent or frequent relapse. Among all used medicine cyclophosphamide is the preferred first line of treatment. Intravenous cyclophosphamide has fewer side effects in comparison to oral route. There has also been significant improvement in steroid response category from steroid dependent to steroid response; frequent relapse to infrequent relapse after use of cyclophosphamide. If no response with cyclophosphamide, other alkylating agents, levamisole, calcineurin inhibitors, mycophenolatemofetil has been considered as an alternative therapy.

Keywords: Children,Cyclophosphamide, Nephrotic syndrome

Nephrotic syndrome is defined by the presence of nephrotic-range proteinuria, edema, and hypoalbuminemia. While nephrotic-range proteinuria in adults is characterized by protein excretion of 3.5 g or more per day, in children it is defined as protein excretion of more than 40 mg/m^2/24h or a first-morning urine protein/creatinine of 2 mg/mg creatinine or greater. Frequently relapsing nephrotic syndrome (FRNS) is defined as steroid-sensitive nephrotic syndrome (SSNS) with 2 or more relapses within 6 months, or 3 or more relapses within a 12-month period. Steroid-dependent nephrotic syndrome (SDNS) is defined as SSNS with 2 or more consecutive relapses during tapering or within 14 days of steroids stopped.

Idiopathic nephrotic syndrome (INS) in children is steroid sensitive in most cases. However, the majority of these will have a relapsing course[1,2] and a significant number are steroid-dependent (SD). Focal segmental glomerulosclerosis (FSGS) is the most frequent cause of steroid-resistant nephroticsyndrome

(SRNS) and End Stage Renal Failure (ESRF) of glomerular origin in children[3]. Patients with minimal change disease (MCD) have a better prognosis, but if they do not respond to steroids, and, in those cases of persistent nephrotic proteinuria, the long-term evolution is similar [4,5]. There is a high incidence of steroid side effects in SD patients[6,7]. Although corticosteroids have reduced mortality of SSNS to less than 5%[8] repeated courses of steroid therapy have potential serious adverse effects such as obesity, poor growth, hypertension, osteoporosis, and diabetes mellitus[9]. Steroid sparing agents, such as levamisole, calcineurin antagonists, and mycophenolic acid, have been reported to reduce the number of relapses and to allow low doses or even withdrawal of steroids, but do not clearly display a long-term effect[10]. Furthermore, the withdrawal of these drugs is usually associated with a relapse of nephrotic syndrome without any significant change in the level of steroid dependence[11]. In contrast, a course of cyclophosphamide (CPO) treatment could lead to long-lasting remission[12] or at least to a reduction in the number of relapses or of the level of steroid dependence[13]. The side effects of cyclophosphamide such as bone marrow suppression[14,15], gonadal toxicity[16] and possibly oncogenicity[17] seem to be dose related.

Steroid-dependent (SD) nephrotic syndrome:

In a randomized controlled trial, effectiveness of IVCP versus OCP to evaluate its usefulness in patients with SD nephrotic syndrome was performed.A total of 47 children with SD INS were enrolled in the study. Of these, IVCP was given to 26 children and OCP to 21 children. In the IVCP group, cyclophosphamide was started at a dose of 500 mg/m2 per month IV for 6 months after achieving a steroid-induced remission, i.e., a cumulative dose of 3,000 mg/m2 or 100 mg/kg. The drug was dissolved in 300 ml of normal saline and infused over 3 h; In the OCP group, cyclophosphamide was given at a dose of 2 mg/kg body weight daily for 12 weeks (a cumulative dose of 180 mg/kg). In the IVCP group, 15 of 26 (57.7%) patients achieved sustained remission compared with 5 of 21 (23.8%) patients in the OCP group; Another 3 of 26 (11.5%) patients in the IVCP group remained SD after therapy compared with 9 of 21 (42.8%) patients after OCP therapy. Overall, 23 of 26 (88.5%) patients improved their steroid response categories from SD to sustained remission, infrequent relapser, and frequent relapser in the IVCP group compared with 12 of 21 (57.1%) in the OCP group[6]. Another retrospective studybetween 1994-2007 reported byAzib et al[10]. Ninety patients (67 boys and 23 girls) with idiopathic nephrotic syndrome (INS) were included and treated by a single course of oral CPO; these patients underwent a 2 mg/kg/day CPO treatment over 10–12 weeks. After CPO treatment, steroids were discontinued in 45 patients over a median period of 0.9 years. The percentage of patients in complete remission after CPO treatment was 57% at 1 year, 42% at 2 years, and 31% at 5 years. More than 80% of relapses occurred within 2 years of CPO initiation and no patients relapsed after 4.5 years in remission[10].Chen et al. [18] reported a retrospective review of the medical records of forty-six patients (33 boys, 13 girls) with SDNS who were treated in Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan, between January 1994 and December 2006 was done. Cyclophosphamide was administered

at 2–3 mg/kg/day for 8 weeks. One course of cyclophosphamide resulted in 17 children (37%) with complete remission and four (9%) shifting to SSNS. Fourteen children (30%) were disease-free for a mean of 7.8 months (2–23 months), although SDNS later recurred. The steroid threshold was decreased in seven children (15%). Four children (9%) had no response to cyclophosphamide.

Steroid-sensitive Nephrotic Syndrome:

Esfahan et al.[9] reported that ther retrospective study with 226 patients with INS, treatment was with corticosteroids, 38 (16.8%) had no relapse but the remaining 188 (83.2%) patients experienced several relapses, of which 128 patients (56.6%) required additional immunosuppressive agents for satisfactory control of NS. Of these, 124 (96.8%) were treated with levamisole, 22 (17%) with cyclosporine, 36 (28.1%) with cyclophosphamide, and ten (7.8 %) were treated with mycophenolatemofetil. Levamisole was effective as a steroid-sparing drug in 103 (83%) of patients, but only 43 (35%) remained in long-term remission after the drug cessation. Long-term remissions were observed in 13 patients (36.1%) receiving cyclophosphamide. Cyclophosphamide 2.5mg/kg/day for 8 weeks was used.Another retrospective study with 106 patients (71 boys and 35 girls, >95% Caucasians) who have been treated with CPO in the years 1971 through 2000 were included. Cyclophosphamide 2mg/kg/day for 10-12 weeks were used; the percentage of patients in complete remission was 44%, 34%, and 24% after 1, 2, and 10 years, respectively. More than 90% of all relapses occurred within 2 years and no patient relapsed after 5 years in remission. Patients with FRNS had a significantly higher remission rate than patients with SDNS (54% versus 17% after 5 years)[19].

Steroid-resistant Nephrotic Syndrome:

Immunosuppressant agents should be used in all SRNS children. Bhimmaet al.[20] reported a retrospective study at King Edward VIII Hospital, Durban, South Africa, during the period 1976–June 2004. Two hundred and twenty-three children with idiopathic SRNS were enrolled, among which 116 were Indian children, 73 (62.9%) had a course of prednisone and oral cyclophosphamide therapy, 32 (43.8%) achieved complete remission. In total, 61 (52.6%) Indian children responded to a course of prednisone and oral cyclophosphamide treatment. Of the 23 black children who received prednisone and oral cyclophosphamide, 2 (8.7%) initially responded but subsequently relapsed. Patients with minimal-change NS were more likely to go into complete remission using prednisone and oral cyclophosphamide (66.6%), compared to those with FSGS (40.9%), proliferative disease (13.3%) or those with indeterminate histology (25.0%); Fifty (27.3%) patients received oral steroid and cyclophosphamide; 117 (63.9%) others who failed this treatment received pulse doses of intravenous methylprednisolone and oral cyclophosphamide, 10 (5.5%) received pulses of intravenous methyprednisolone and cyclophosphamide in combination with oral steroids (4 of these patients had failed pulse doses of methyprednisolone and oral cyclophosphamide) and 6 (3.3%) received oral cyclosporin. Initially all patients were given oral prednisone (2 mg/kg, maximum 60 mg) for 6 weeks followed by the same dose on alternate days for another 6 weeks and reduced to none over 2.5 months.

Failure to respond was taken as steroid resistance. Second line treatment included low-dose oral prednisone (0.1–0.3 mg/kg) given on alternate days with a daily dose of oral cyclophosphamide (2–3 mg/kg) for 8–12 weeks. Black children were more likely to be treated with intensive therapy because of failure to respond to oral steroids and cyclophosphamide compared to Indian children 84 (84.8%) vs. 49 (58.3%).Another retrospective study, since 1990, all children suffering from SRNS, 16 girls and 14 boys, in La Paz Children's Hospital in Madrid, were treated under a protocol of MP pulses (30 mg/kg, maximum 1 g, diluted in 50–100 ml of solution with 5% glucose during a period of 2 h to 4 h) in conjunction with orally administered prednisone (2mg/kg, alternate days) were included. At the beginning six pulses were administered on alternate days, followed by a weekly pulse for 2 months, a pulse every 2 weeks for 2 months, a monthly pulse for 8 months, and a pulse every 2 months over the next 6 months. After the completion of the pulse programme, the oral dose of prednisone was reduced progressively and was suspended after 6–18 months; if a relapse was noted after the frequency of pulses had been diminished; oral treatment with cyclophosphamide (2–3 mg/kg/day for 8–12 weeks) was added together with weekly pulses. Total NS remission was achieved in 22 patients (73.3%): ten patients only with MP pulses and 12 by the addition of cyclophosphamide (CP). Partial response was achieved in three children and no response in five[3].

Frequently-relapsing Idiopathic Nephrotic Syndrome:

A prospective study was conducted with total of 51 children with either FR or SD INS, of these 22 was FR and 29 were SD. The patients were given oral prednisolone 60mg/m2/day for 2 weeks or until they had been in remission for 3 days, and they were then given 40mg/m2 on alternate days for 4 weeks tapering off over the next 4 weeks. IVCP was started in a dose of 500mg/m2/month for 6 months after achieving a steroid induced remission. The drug was dissolved in 300 ml of 5% dextrose and infusion over 3 hour. FR group 15(67.5%) patients achieved a prolonged remission, 4(18%) improved and became IFR, while another 3(13.6%) patients remained FR despite IVCP therapy. In the SD group 12(41%) patients achieved a prolonged remission, 9(31%) improved to IFR status 5(17%) turned FR and 3(10%) remained SD despite IVCP. After a mean follow up of 27+/_21 months after the last dose of IVCP, of the 51 patients 27(51%) achieved sustained remission, 13(25%) became IFR, 8(16%) were FR while 3(6%) remained SD. The number of children in FR group who achieved a sustained remission (15/22) was similar to that in the SD group (12/29)[21].

Side effects of Cyclophosphamide:

The incidence of side effects was higher with OCP than IVCP. Alopecia was more common in the OCP group and reversed on completion of therapy in both groups. Leukopenia was also more common in the OCP group[6].Minor side effects included weight gain, hypertension, abdominal pain from possible gastric erosions; mild hair loss and bluish discoloration of the nails were also noted during treatment. More serious adverse effects, possibly related to treatment, included severe infections septicaemia and chickenpox and

end-stage renal failure that underwent dialysis was also noted[20].

Is Biopsy required prior to Cyclophosphamide therapy?

Biopsy whether should be done or not in INS children prior to cyclophosphamide therapy remains controversial, however, most pediatric nephrologists consider that it is usually not necessary. In a study renal biopsy in 51 children with FRSSNS was performed prior to cyclophosphamide therapy, no correlation between pre-biopsy course and histology and post cyclophosphamide course was noted, steroid sensitivity rather than histology is determinant of prognosis, frequency of relapse alone is not indication of biopsy[22].Stadermannet al. [23] documented their study that 85 children with FRSSNS/SDSSNS, biopsy prior to eight week cyclophosphamide was done and concluded that no biopsy is required prior to cytotoxic therapy in uncomplicated SSNS.Another study conducted shows biopsy is usually not necessary in patients with frequent relapses or steroid dependence before starting treatment with levamisole, cyclophosphamide or MMF[24]. In another study biopsy of 18 patients with SDSSNS followed by 12 week cyclophosphamide with or without steroid, histology showed MCNS in 14 and MCNS + IgM in 4 cases with no influence on treatment and concluded that biopsy is not required prior to cyclophosphamide[25].

CONCLUSION

The best way to treat children with INS who do not respond after at least 4-6 weeks of oral prednisone administration is not clear. Many immunosuppressive drugs have been suggested; cyclophosphamide has been the drug of choice for first line of treatment. Both oral and IVCP has been used for treatment. In older children period of remission is prolonged in comparison of younger children; which shows age as a significant factor for prolonged remission. IVCP is an effective form of therapy for SD INS patients. IVCP has less or no side effect in comparison to oral cyclophosphamide. The patients receiving IVCP has a significant improvement in steroid response categories from SD to sustained remission, infrequent relapse, and frequent relapse. Biopsy is not mandatory prior cyclophosphamide.

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