ORIGINAL ARTICLE

Prolonged Initial Phase Tapering Prednisolone Therapy In Nephrotic Syndrome

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ABSTRACT

Objective: To assess the prospects of maintaining a sustained remission by prolonged initial phase steroid therapy in nephrotic syndrome.

Design: Hospital based descriptive study.

Place and Duration: Department of Pediatric Medicine, Combined Military Hospital, Lahore, Pakistan. January 2002 to January 2010.

Patients and Methods: Fifty children of both genders in their very first episode of steroid sensitive nephrotic syndrome (SSNS) were selected after an informed parental consent. Prednisolone was used in a gradually tapering dose spread over 7 months with a post-treatment 12-month follow up. Albuminuria was monitored by dipstick method.

Results: Thirty five (70%) boys and 15 (30%) girls participated in the study with male to female ratio of 2.3:1. Mean age was 4.62±2.15 years. All the patients became albuminuria-free within first 4 weeks of treatment. Thirty two (64%) patients maintained remission during the study and 12-month follow-up period. Eighteen (36%) case relapsed within 6 months after completion of initial treatment. Eight (16%) of these 18 cases had multiple relapses. Cushingoid appearance and mild hypertrichosis was noted in all the 50 (100%) cases.

Conclusion: Prolonged initial phase tapering steroid therapy helps maintain a sustained and longer remission in SSNS. It should be adopted as the standard regimen.

Key Words: Nephrotic Syndrome, Prolonged Steroid Therapy

INTRODUCTION

Corticosteroids have remained the first line of defence in the treatment of children with steroid sensitive nephrotic syndrome (SSNS) since 1950s. The general consensus is that up to 90% of children in their initial presentation respond well to steroid therapy as an over whelming majority (76.6%) of these patients supposedly has minimal change nephrotic syndrome (MCNS) [1, 2]. In fact, the term 'MCNS' is now gradually getting synonymous with SSNS as far as the responsiveness to steroids is concerned [3]. But SSNS is known to be a potentially relapsing disease and more recent evidence suggests that following an 8-week treatment with steroids, up to 70% of the patients are likely to relapse. Boys below 4 years at the onset are more likely to experience frequent relapses and a longer time interval to achieve sustained and permanent remission [3, 4, 5, 14]. The tendency to relapse frequently has led to a number of controlled trials comparing the conventional 8-week protocol with longer duration of steroid regimen (3-7 months) including 4-8 weeks of daily prednisolone followed by a tapering and alternate-day schedule [6, 7, 12]. The duration of initial steroid therapy influences the risk of relapse. With a 2-year follow-up, clinically significant reduction in the relapse rate by 25-33% has been observed with prednisolone regimen of three months duration or longer. Statistically, a longer duration (3-7 Months) of prednisolone decreases the number of children with frequent relapses. The duration of treatment appears more important than the overall total dose of prednisolone in reducing the risk of relapse. There is a relative risk reduction of 13% for every additional month of treatment up to 7 months [2, 8]. This study was carried out to aim at the prospects of using corticosteroid therapy for an extended period of seven months in an attempt to decrease the relapsing tendency of our SSNS patients.

PATIENTS AND METHODS

This descriptive study was completed at the Department of Pediatrics, Combined Military Hospital Lahore, Pakistan from January 2002 to January 2010. Fifty children in their very first episode of SSNS were included in the study.

Exclusion criteria: 1. Age below 1 and above 10 years. 2. Those showing steroid resistance or dependence. 3. Previous treatment with steroids and cytotoxic drugs. All patients were subjected to a detailed history, physical examination and the relevant laboratory work-up. None of the patients manifested hypertension, gross hematuria or hypocomplementemia. Parental co-operation was encouraged to monitor albuminuria daily in the first morning-urine specimen by dipstick method (Albustix/Uristix). Albuminuria chart was maintained in each case. In addition to other supportive treatment, all the patients were treated by a 7-month long Prednisolone regimen of 60 mg/m^2/day for 4 weeks followed by 40 mg/m^2 on alternate days for 4 weeks, administered as single dose in the morning and then gradually tapered off over the remaining 5 months by an alternate-day schedule. Each child was monitored as an out-patient every 2-4 weeks during the study and the post-treatment 12-month period. The nominal variables were reported as frequency/percentage and analyzed by using Chi-square test while numerical data was expressed as Mean ± standard deviation (SD). Operational Definitions: SSNS: complete remission is achieved within 4 weeks of Prednisolone therapy in a dose of 60 mg/m^2/day. Steroid Resistant Nephrotic Syndrome (SRNS): failure to achieve remission within 4 weeks of Prednisolone therapy in a dose of 60 mg/m^2/day. Remission: albuminuria nil or trace by dipstick or proteinuria <4 mg/m^2/h in 3 consecutive first morning specimens. Relapse: urine albumin 3+ or 4+ by dipstick or proteinuria >40 mg/m^2/h in 3 consecutive first morning specimens, having been in remission previously.

RESULTS

Of 50 patients included in the study, there were 35 (70%) boys and 15 (30%) girls. Male to female ratio was 2.3:1. Their ages ranged from 1.8 to 10 years with Mean ±SD 4.62 ±2.15 years. Within the initial 4-week prednisolone therapy, complete remission was documented in each of the 50 (100%) cases. Thirty two patients (64%) were able to maintain a sustained remission and did not experience relapse during the study period and the post-treatment follow-up of 12 months. Eighteen patients (36%) relapsed within the first 6 months after they had completed the initial treatment. Ten (20%) of the cases relapsed only for once. Eight (16%) patients relapsed more than once over the 12-month follow-up; of which 3 (6%) cases had 2 relapses, 3 (6%) cases relapsed thrice and 2 (4%) patients relapsed 4 times. Relapses in 13 (26%) cases particularly including those who had multiple relapses were apparently triggered by upper respiratory viral infections. Except a cushingoid appearance and mild hypertrichosis in almost all the 50 (100%) cases, no other steroid related adverse effects were observed. Early post-treatment relapse strongly indicated a tendency to relapse frequently in the due course of time [Table 1 & 2].

Table 1: Outcome of 7-month tapering prednisolone therapy (n=50)

Sustained remission during study and Follow-up (19 months)	32 (64%)
Relapse within 6 months after initial therapy	18 (36%)
Multiple relapses during 19 months	8 (16%)
Cushingoid facies and Hypertrichosis	50 (100%)

Table 2: Distribution of relapsing cases (n=18)

No: of patients	10 (20%)	3 (6%)	3 (6%)	2 (4%)
No: of relapses	1	2	3	4

DISCUSSION

The International study of Kidney Disease in Children (ISKDC) regimen recommends prednisolone 60 mg/m^2/day with a maximum dose of up to 80 mg/day in divided doses for 4 weeks followed by 40 mg/m^2/day with a maximum of 60 mg/day in divided doses on 3 consecutive days/ week for 4 weeks. The Arbeitsgemeinscht fur

Padiatrische Nephrologie (APN) regimen suggested that instead of 3 consecutive days/week, an alternate day prednisolone 40 mg/m^2 for 4 weeks resulted in a significantly lower number of patients with relapses and relatively fewer relapses per patient. It also suggested that prednisolone could be administered as a single morning dose on alternate days rather than in divided doses [2, 9]. Due to the high relapsing tendency in SSNS patients, since the last decade or so, an extended corticosteroid treatment has been used particularly in the first episode of nephrotic syndrome to reduce the relapse rate. The pioneer study by APN in this context reported a lower relapse rate from 62 to 36% in a period of 12 months. The patients in the APN study were treated with 60 mg/m^2 prednisolone daily for 6 weeks followed by 40 mg/m^2 prednisolone on alternate days for 6 weeks as compared to the ISKDC's standard 8-week treatment [9]. Although the present published standard duration of Prednisolone treatment is 8-12 weeks but now most of the authors have recommended 12 weeks [10]. Bagga in 2008 published revised guidelines for the management of SSNS and proposed that the benefit and safety of prolonged steroid therapy, beyond the recommended duration of 12 weeks, requires further studies [11]. An extended and slow tapering phase of steroid treatment helps maintain long term remission because moderate to severe adrenal suppression as a result of high dose steroid therapy has been directly implicated in an increased risk of relapse (16, 17). A longer duration (3-7 months) of corticosteroid treatment of children in their first episode of SSNS results in a significantly reduced risk of relapse at 12 and 24 months (from 60% to 33%) and without any increased steroid related toxicity as shown in a meta-analysis of five randomized controlled trials. Contrary to the common belief, prolonged tapering steroid therapy in various studies has not shown any increased risk of glucocorticoid toxicity [7, 12, 15, 19, 20]. ALT MA, et al (2009) were able to achieve a statistically significant reduction in relapse rate (from 75% to 30%) with a higher percentage of sustained remission and concluded that 6-month corticosteroid therapy may be preferable to standard 2-month course for the initial treatment of SSNS in children [18]. A prolonged course of prednisolone therapy for an initial episode of nephrotic syndrome reduces the relapse rate without increasing the risk of steroid related adverse effects. The prolonged initial phase therapy may be particularly useful in developing countries where frequent infections often induce early relapses [21, 22, 23, 24, 25, 26, 27]. Relapses in nephrotic syndrome are often triggered by upper respiratory tract viral infections, possibly mediated by cytokine release. If Prednisolone is prescribed daily for 7 consecutive days at the same dose as taken by the patient on an alternate-day schedule at the onset of a possible viral infection, it significantly reduces the risk of relapse [28]. By using 7-month long tapering prednisolone regimen, we were able to achieve a complete and sustained remission in 64% of our SSNS patients in their very first episode without any significant steroid toxicity [Table 1 & 2]. Our results are generally comparable and co-relate well with the international literature on the subject. Local literature on this issue is not available so far. Currently, there is no clinical data to suggest any beneficial effect if the Prednisolone treatment is extended beyond 7 months.

CONCLUSION

Based on the available data, we conclude that a 7-month long initial phase tapering steroid therapy for SSNS helps maintain a longer sustained remission and a clinically significant reduction in the relapse rate. It is, therefore, recommended that the 7-month Prednisolone regimen deserves to be adopted as a standard treatment protocol.

REFERENCES

1. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children. Kidney Int; 1978: 13(2): 159-65.
2. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisolone. A report of the International study of Kidney Disease in Children. J Pediatr 1981; 98(A):561-4.
3. Bagga A, Mantan M. Nephrotic syndrome in children. Indian J Med Res 2005; 122: 13-28.
4. Hiraoka M, Tsukahara H, Haruki S, Hayashi S, Takeda N, Miyaqawa K, Okuhara K, Suehiro F, Mayumi M. Older boys benefit from higher initial prednisolone therapy for nephrotic syndrome. The West Japan Co-operative Study of Kidney Disease in Children. Kidney Int 2000; 58: 1247-52.

5. Lewis MA, Baildom EM, Davis N, Houston IB, Postlethwaite RJ. Nephrotic syndrome: from toddlers to twenties. Lancet 1989; 1: 255-9.
6. Ueda N, Chihara M, Kawaguchi S, Niinomi Y, Nonoda T, Matsumoto J. Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. J Pediatr 1998; 112(1): 122-6.
7. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Sys Rev 2000; 83: 45-51.
8. Bagga A, Hari P, Srivasatava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. Pediatr Nephrol 1999; 13(9): 824-7.
9. Alternate-day versus intermittent prednisolone in frequently relapsing nephrotic syndrome. A report of “Arbetsgemeinschaft fur Padiatische Nephrologie”. Lancet 1979; 1(8113): 401-3.
10. Hogg RJ, Portman RJ, Milliner D, Lemley KD, Eddy A, Ingelfinnger J. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection and elimination (PARADE). Pediatrics 2000; 105: 1242-9.
11. Bagga A. Revised guidelines for management of steroid sensitive nephrotic syndrome. Indian J Nephrol 2008; 18(1): 31-9
12. Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Sys Rev 2007; (4): CD001533.
13. Kabuki N, Okugawa T, Hayakawa H, Tomizawa S, Kasahara T, Uchiyama M. Influence of age at onset on the outcome of steroid-sensitive nephrotic syndrome. Pediatr Nephrol 1998; 12(6): 467-70.
14. Andersen RS, Thrane N, Noergaard K, Jespersen B, Rittig S. Early age at debut is a predictor of steroid dependent and frequently relapsing nephrotic syndrome. Pediatr Nephrol 2010; 25(7): 1299-304.
15. Hiraoka M, Tsurusawa M, Takeda N, Haruki S, Hayashi S, Ohta K, Momoi T, Ohshima Y, Suqanuma N, Mayumi M. A randomized study of two long-course prednisolone regimens for nephrotic syndrome in children. Am J Kidney Dis 2003; 41(6): 1156-62.
16. Leisti S, Koskimies O, Perheentupa J, Rapola J, Viska J. Association of postmedication hypocortisolism with early first relapse of idiopathic nephrotic syndrome. Lancet 1977; 2(8042): 795-6.
17. Abeyagunawardena As, Hindmarsh P, Trompter RS. Adrenocortical suppression increases the risk of relapse in nephrotic syndrome. Arch Dis Child 2007; 92(7): 585-8.
18. ALT MA, ETL SOO, PC TONG, WM LAI, KC TSE, MC CHIU. Long versus standard course corticosteroid therapy for nephrotic syndrome in children. HK J Pediatr (new series) 2009; 14: 103-7.
19. Mishra OP, Thakur N, Mishra RN, Prasad R. Prolonged versus standard prednisolone therapy for initial episode of idiopathic nephrotic syndrome. J Nephrol 2011; doi: 10.5301/jn. 5000016. [Epub ahead of print]
20. Ksiazek J, Wyszyriska T. Short versus long initial prednisone treatment in steroid-sensitive nephrotic syndrome. Acta Pediatr 1995; 84(8): 889-93.
21. Bagga A, Hari P, Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. Pediatr Nephrol 1999; 13(9): 824-7.
22. Hogg RJ, Gauthier B, Shah B, Leonard MB, Bonilla-Felix M, Nash M, Roy S 3rd, Strife CF, Arbus G. Long versus standard initial steroid therapy for children with nephrotic syndrome: a report from the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol 2003; 18(4): 342-6.
23. Ueda N, Chihara M, Kawaguchi S, Niinomi Y, Matsumoto J, Ohnishi M, Yasaki T. Intermittent versus long-term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. J Pediatr 1988; 112(1): 122-6.
24. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinschaft fur Padiatrische Nephrologie. Eur J Pediatr 1993; 152(4): 357-61.
25. Norero C, Delucchi A, Lagos E, Rosati p. Initial therapy of primary nephrotic syndrome in children: evaluation in a period of 18 months of two prednisone treatment schedules. Chilean Co-operative group of Study of Nephrotic Syndrome in Children. Rev Med Chil 1996; 124(5): 567-72.

26. Ksiazek J, Wysznska T. Short versus long initial prednisone treatment in steroid-sensitive nephrotic syndrome in children. Acta Pediatr 1995; 84(8): 889-93.
27. Lande MB, Gullion C, Hogg RJ, Gauthier B, Shah B, Leonard MB, Bonilla-Felix M, Nash M, Roy S 3rd, Strife CF, Arbus G. Long versus standard initial steroid therapy for children with nephrotic syndrome: A Report from the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol 2003; 18(4): 342-6.
28. Abeyagunawardena AS, Tromptre RS. Increasing the dose of prednisolone during viral infections reduces the risk of relapse in nephrotic syndrome: a randomized controlled trial. Arch Dis Child 2008; 93(3): 226-8.