Management of Nephrotic Syndrome: ISKDC versus APN

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ABSTRACT

Objective: To compare the frequency of relapses between ISKDC and APN protocol in the treatment of Nephrotic syndrome.
Study design: Randomised Control Trial.
etting: Department of Paediatrics, Sandeman Provincial Hospital Quetta, and Balochistan**.**
Duration: One year.
Methodology: Total 92 patients, 46 patients in each group, were selected according to non probability purposive sampling including all nephrotic patients age 1 to 16 years keeping in mind the confounders, then allocating them into group 1 receiving ISKDC and group 2 (APN) randomly and following them for a year. First relapse was the end point of study.
Results In group 1, 4% of patients relapsed by first month, 13% by three months, 35% by six months, and 72 % by one year. In group 2 no patient relapsed by first month, 2% by 3 months, 15% by six months, and 30% by one year. The P value was 0.026. The longer duration of steroids was significant in reducing the risk of relapse at the end of study (relative risk 0.72) (95% CI 0.60-0.90).
Conclusion: APN is superior to ISKDC in preventing relapses in nephrotic syndrome.
Key words: Nephrotic, APN, ISKDC, Relapse

INTRODUCTION

The term nephrotic syndrome is only fifty to sixty years old, but it has been known to man since ancient times[1]. Hippocrates was first to recognize oedema (puffy eyelids) as a manifestation of renal disorder although he did not dilate on its different causes.[2] However the first detailed description of idiopathic nephrotic children is seen in the works of MJC Sabatier.[1] (29%) of admitted patients with renal disease had nephrotic syndrome in a study from Pakistan.[3] Nephrotic syndrome is an important chronic disease in children, characterized by minimal change disease in the majority[4]. The response to corticosteroid therapy is the best prognostic marker of the disease.[5,6] Initial episodes of the nephrotic syndrome are best treated with "long" courses of prednisone therapy (6 wk of high-dose daily prednisone followed by 6 wk of alternate-day prednisone).[7] Various protocols have been suggested for treatment of nephrotic syndrome i.e. ISKDC and APN. Hodson in his meta-analysis concluded that children in their first episode of steroid responsive nephrotic syndrome should be treated with prednisone for at least three months, with an increase in benefit being shown for up to seven months of treatment.[8] This study compares two protocols of ISKDC versus APN in the treatment of nephrotic syndrome as regards efficacy and treatment side effects.

PATIENTS AND METHODS

This was a randomised Control Trial conducted at Paediatrics Department Sandeman Provincial Hospital Quetta, Balochistan and lasted for One Year. A total of 92 patients with 46 patients in each group selected via non-probability purposive sampling. The patients included in this study were between 1 to 16 years with first manifestation of Nephrotic syndrome, or patients with infrequent relapsing Nephrotic syndrome (<4relapses within 12 months). The following patients were excluded from the study: Frequent relapsers (>4/year), steroid dependent nephrotic syndrome, Steroid resistant Nephrotic syndrome, and patients with secondary Nephrotic syndrome. The mode of admission was through OPD. Patients were diagnosed based on history, examination, heavy proteinuria >40mg/m^2/day, hypoalbuminemia <2.5g/dl, oedema, hypercholesterolemia (250mg/dl), and GFR of > 90ml/min/m2. Informed written consent from the parents of selected patients was obtained. Patients were divided randomly to exclude selection bias. Group I received steroids as per "ISKDC protocol " i.e. daily steroid in dose of 60mg/m2/day for four

weeks followed by alternate day steroid 40mg/m^2/day for four weeks then stopped abruptly. Group II received steroids as per "APN protocol" i.e. daily steroid in the dose of 60mg/m^2/day for six weeks followed by alternate day steroid 40mg/m2/day for six weeks then stopped abruptly. Clinical follow-up was done monthly for a year and first relapse was the end point of the study. Comparison of two treatments to determine the frequency of relapse was done by certain criteria like the recurrence of proteinuria, hypoalbuminemia, and oedema (detected periorbital and pedal), frequency of complications of therapy and mortality.

The data was analysed by SPSS version 10.0. Descriptive statistics like mean±standard deviation were calculated for variables like age, weight, serum albumin and urinary protein. Frequency of the study variables i.e. the relapse in Nephrotic syndrome in the two groups was calculated. The difference of the frequency of relapse in the two groups was tested statistically to see whether the difference was statistically significant or not. The P value of ≤0.05 was taken as significant.

RESULTS

The age distribution between the two groups is shown in Table 1. The P value was 0.15. The sex distribution between the two groups is shown in graph one. The mean body weight distribution between the two groups is shown in Table 2. P value was 0.36. In group 1 (ISKDC), 65% developed swelling with in five-day days of presentation, 30% within 10 days of presentation, and 4% presented after ten days of presentation. The mean was 1.41days with a standard deviation of 0.57. While in group 2 (APN) 72% developed swelling within five days of presentation, 24% developed swelling with in ten days while 4.3% complained of swelling lasting more then ten days. The mean was 1.47 days with a standard deviation of 0.58. In group 1 (ISKDC), 100% of the children presented with periorbital oedema, 70% presented with pedal oedema in addition to periorbital oedema while 4.3 % presented with sacral oedema too. In group 2 (APN) 96% presented with periorbital oedema, 65% presented with pedal oedema, while 4.3 % presented with sacral oedema too**.** The mean systolic blood pressure in group 1 was 110.52±8.94, while the diastolic blood pressure was 71.53±6.37. The mean systolic blood pressure in-group 2 was 114.12±9.27 and the mean diastolic blood pressure was 75.52± 7.46. The P value for systolic blood pressure 0.08 and for diastolic blood pressure was 0.11. In group 1, 9 % of patients had serum albumin l less than 1 g/L, 48 % had serum albumin less the 2 g/L but more than 1 g/L, and 43% had serum albumin more the 2 g/L but less than 3 g/L. None of the patients had serum albumin more than 3 g/L. The mean was 2.35 g/L with a standard deviation of 0.64 (CI of 2.16 to 2.49). In Group 2, 13 % had serum albumin less than 1 g/L, 46% had serum albumin less than 2 g/L but more than 1 g/L, and 41% had serum albumin less than 3 g/L but more than 2 g/L. Like group 1 none had serum albumin more than 3 g/L. The mean was 2.40 g/L with a standard deviation of 0.61 and (CI of 2.08 to 2.54). In group 1, 17 % of children had 2+ proteins in urine, 65 % had 3+ proteins in urine, and while 17% had 4+ proteins in urine .The mean was 2.92 with a standard deviation of 0.65. In group 2, 21. 7% had 2+ proteins in urine, 63 % had proteins 3+, 15 % had 4+ proteins in urine.

Table 1: Distribution of children of different age groups in Group 1 (ISKDC) and Group 2 (APN)

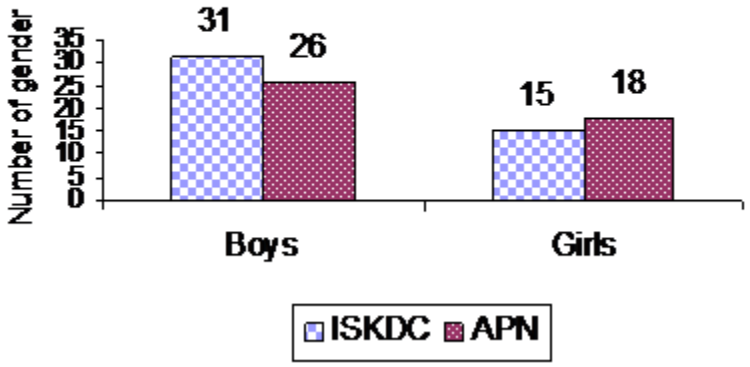
Age (Years)	**Group 1 (ISKDC) (n=46)**		**Group 2 (APN) (n=46)**	
	No.	**%**	**No.**	**%**
<5	19	41.4	21	45.7
6 – 8	22	47.8	20	43.5
9 -12	3	6.5	3	6.5
13 – 16	2	4.3	2	4.3
Mean±SD	5.97±2.56		5.76±3.03	

Table 2: Mean body weight in both groups

Groups (Protocol)	**Mean**	**Standard deviation**	**CI >95%**	
			Lower bound	**Upper bound**
Group 1 (ISKDC)	19.41	4.68	18.02	20.80
Group 2 (APN)	19.53	5.72	18.02	20.80

Total	19.53	5.20	17.95	21.35

Fig.1: Distribution of boys and girls in Group 1 (ISKDC) & Group 2 (APN)



The mean was 2.86 with a standard deviation of 0.61. As far as relapse is concerned, in group 1(ISKDC), 4% of patients relapsed in first month; further 9% relapsed by three months making the total relapse at 13%. By six months 22% patients relapsed and the total relapse reached 35%. By the end of one year 36% more patients had relapsed, making the total percentage of relapsed patients at 72%. In group 2 (APN), no patient relapses by the end of first month, while 4% patients relapsed by 3 months, 11% more patients had relapsed by six months, making the total 15%. Further 13% had relapsed by one year, and a total of 28% patients who had relapsed. In group 1 (ISKDC), 28% patients did not relapse, while 70% patients did not relapse in group 2 (APN) and the P value was 0.026. The P value in those who had relapsed was 0.027. The longer duration of steroids was significant in reducing the risk of relapse at the end of study (relative risk 0.72) (95%confidence interval 0.60-0.90). The total cumulative dose in mg in group 1 was 2.07, while in group 2 was 3.02 giving the p value of <0.05. (.002). In group 2 (APN), 5 % of patients developed cushingoid appearance, and 3% of the patients developed hypertension. No complications were noted in group 1 (ISKDC).

DISCUSSION

There was a difference between the ages of the two groups, the first group being slightly older, but this difference was not found to be statistically significant. This age was slightly different from other studies conducted in Asia[9] but this may be because of slightly late presentation in this province. Further research is needed to prove this, but the study mentioned above was retrospective while our study was prospective. Boys presented more commonly then girls, in both groups. That may be because of gender bias as boys are brought early to medical attention in our culture. But it may be due to the fact that it is more frequent in boys. What is of importance is that this is also seen in studies done internationally. But it was not found to be statistically significant in our study. Likewise it was also found to be insignificant in other studies as well[10,11]. The mean body weight in the two groups was not found to be statistically significant and this is consistent with other international studies[11].

There was no difference in the two groups as regards the mean duration of presentation of edema or the site of edema. Group two had a slightly higher blood pressure then group one, but it can't be explained on the basis of ingestion of steroids, since they were started after the evaluation was complete. And this difference was not found to be statistically significant too. Serum albumin was comparable between the two groups, as were the urinary proteins and this is in concordance with international studies[10,11].

The frequency of relapse in the two groups that was the thrust of this study was found to be significant. The ISKDC group relapsed twice as much as the APN group. The effect was found irrespective of age and gender. The relapse rate was significantly different in the APN and ISKDC groups (0% vs. 4% at one month, 2% vs. 13% at three months, 15% vs. 35% at 6 months, 30% vs. 72% at one

year time line graph)[10,11]. This goes on to show that nephrotic children who were treated with long course steroid therapy had fewer relapses and were more likely to remain in remission. Our findings are consistent with the previous work showing an inverse relation between the risk of relapse and the duration of corticosteroids therapy.[10-12] Therefore APN is recommended by many centers to treat SSNS for better patient outcome. It must be confessed that the optimal protocol to treat SSNS in still debated and studies are underway. It is hoped that a more innovative and detailed approach will be available in future as research progresses. When APN report came in 1988, (APN 3) the patients who relapsed with ISKDC or standard risk in the first 6 months were higher (61%) compared to APN (31%) then called long course regimen.[9] Then many other studies in the late eighties and early nineties also proved the same point. Finally in his historic Meta analysis Hodson et al[11] reported that the combined results from these studies allowed a recommendation that the initial treatment with SSNS should be at least 3 months. All these are consistent with our study. This study was conducted over a period of one year as compared to other studies that evaluated the relapse rate over six months. Our study is significant that unlike other studies this is a prospective study, and the two groups compared were similar in their clinical characteristics, serum albumin, blood pressure etc.

CONCLUSION

APN is superior to ISKDC in preventing the relapse in children with nephrotic syndrome.

REFERENCES

1. Richet G. Clinical nephrology in the European French-speaking countries from 1945 to 1960: a physiopathological tradition. Nephrologie Therap 2009, 5(3): 210-3.
2. Angeletti LR, Cavarra B: Critical and historical approach to Theophilus' De Urinis. Urine as blood's percolation made by the kidney and uroscopy in the middle ages. American journal of nephrology 1994, 14(4-6):282-289.
3. Iqbal J, Rehman MA, Khan MA: Pattern of renal disease in children. JPMA 1994, 44(5): 118-20.
4. Bagga A, Mantan M. Nephrotic syndrome in children. Indian J Med Resh 2005, 122(1): 13-28.
5. Peco-Antic A. Management of idiopathic nephrotic syndrome in childhood. Srpski arhiv za celokupno lekarstvo 2004; 132(9-10): 352-9.
6. Ksiazek J, Wyszynska T. Short versus long initial prednisone treatment in steroid-sensitive nephrotic syndrome in children. Acta Paediatr 1995; 84(8): 889-93.
7. Mendoza SA, Tune BM. Treatment of childhood nephrotic syndrome. J Am Soc Nephrol 1992; 3(4): 889-94.
8. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy in nephrotic syndrome: a meta-analysis of randomised controlled trials. Arch Dis Childhood 2000; 83(1): 45-51.
9. Short versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Lancet 1988; 1(8582): 380-3.
10. Ehrich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Eur J Pediatr 1993; 152(4): 357-61.
11. Hodson EM, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Sys Rev 2007; 4: CD001533.
12. Noer MS. Predictors of relapse in steroid-sensitive nephrotic syndrome. Southeast Asian J Trop Med Public Health 2005; 36(5): 1313-20.
13. Nephrotic syndrome in children: a randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. Report of the international study of kidney disease in children. J Pediatr 1979; 95(2): 239-43.