Original Articles

Short Term Efficacy of Intravenous Dexamethasone and Methylprednisolone Therapy in Steroid Resistant Nephrotic Syndrome

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Manuscript received: July 11, 2003, Initial review completed: August 14, 2003, Revision accepted: April 7, 2004.

Objective: *To compare the short term efficacy of intravenous pulses of methylprednisolone and dexamethasone in treatment of steroid resistant nephrotic syndrome in children.* ***Methods:*** *We prospectively treated 81 children with idiopathic steroid resistant nephrotic syndrome with six alternate-day pulses of intravenous dexamethasone (5 mg/kg) or methylprednisolone (30 mg/kg). Fifty-nine patients received dexamethasone and 22 were treated with methylprednisolone. Two patients in dexamethasone and one in methylprednisolone group developed serious infection during administration of alternate-day pulses and could not complete the therapy.* ***Results:*** *The median (95% CI) age at treatment was 38 (36-74.7) months. Of patients who completed therapy, 20 (35.1%) (95% CI 22.9-48.9) and 7 (33.1%) (95% CI 14.6-56.9) patients in dexamethasone and methylprednisolone group, respectively achieved complete remission. Following alternate day pu1ses the median urinary albumin to creatinine ratio decreased from 9.2 to 1.5 (P <0.005) in dexamethasone group and from 12.1 to 0.7 (P <0.005) in methylprednisolone group. The median reduction in urinary albumin to creatinine ratio was 54.1% (95% CI 32.7- 83.9) and 63.2% (95% CI 23.5- 100) in dexamethasone and methylprednisolone group respectively. The chief side effects of therapy were transient hypertension or worsening of preexisting hypertension, which occurred in 31 (54.4%) patients in dexamethasone group and 10 (47.6%) in the methylprednisolone group. The hypertension was satisfactorily controlled on antihypertensive drugs. One or more side effects were observed in 66.7% (95% CI 52.9-78.6) children receiving dexamethasone therapy and 61.9% (95% CI 38.4-81.9) receiving methylprednisolone, which was comparable.* ***Conclusions:*** *We conclude that intravenous dexamethasone is as effective as methylprednisolone in inducing remission in patients with steroid resistant nephrotic syndrome.*

Key words: *Focal segmental glomerulosclerosis, Minimal change disease, Proteinuria.*

MAJORITY of patients with idiopathic nephrotic syndrome respond to oral corticosteroids and have excellent long-term prognosis. Approximately 10% of patients are unresponsive to treatment with oral corticosteroids and are referred to as steroid resistant. Patients with steroid resistant nephrotic syndrome (SRNS) with unremitting heavy proteinuria have difficult course and a majority develop chronic renal failure(l). These patients have been treated aggressively with high-dose intravenous corticosteroids with or without oral alkylating agents(2-4), intravenous cyclophosphamide(5) and cyclosporin(6) with variable benefits.

Methylprednisolone is the most widely

used preparation for intravenous corticosteroid therapy for patients with SRNS(4,7), lupus nephritis, crescentic glomerulonephritis(8) and many other life threatening conditions. In view of its easy availability and lower cost of therapy, we have used intravenous dexamethasone as an alternative to methylprednisolone in patients with SRNS(9). There are however, no studies that have prospectively compared the efficacy of intravenous methylprednisolone and dexamethasone in this or related conditions. We report our experience on short-term efficacy of these medications in reducing proteinuria in two cohorts of patients with SRNS.

Subjects and Methods

We prospectively studied all patients aged between 1 and 14 years, with initial or late SRNS who presented to the Pediatric Nephrology services of this hospital between July 1996 and June 2001. Nephrotic syndrome was defined by the presence of hypoalbuminemia (<2.5 g/dL), proteinuria (>40 mg/m^2/hr or urine albumin to creatinine ratio >2) and edema. Initial steroid resistance was considered as failure to respond to treatment with oral prednisolone at a dose of 2 mg/kg daily given for 4 weeks followed by 1.5 mg/kg on alternate days for 4 weeks as defined by International Study for Kidney Disease in 10 children(10). Patients who responded to such therapy initially, but failed to respond to daily oral prednisolone in a subsequent relapse were diagnosed as having late steroid resistance. It is our practice to carry out renal biopsy in all patients of nephrotic syndrome with initial or late steroid resistance.

Patients with renal histopathology other than minimal change disease, focal segmental glomerulosclerosis (FSGS) and mesangioproliferative glomerulonephritis were excluded. Patients who had previously received therapy with intravenous steroids or cyclophosphamide, onset of nephrotic syndrome below 1 year of age or with persistent renal dysfunction (serum creatinine level >1.5 mg/dL) were also excluded. Patients who had serious infections (peritonitis, septicemia, meningitis, septic arthritis or osteomyelitis) during pulse corticosteroid treatment did not receive further pulses. Informed consent was taken from the parents before starting treatment.

We had proposed to randomize patients eligible for the study into two groups to receive either dexamethasone or methylprednisolone. The cost of dexamethasone and methylprednisolone injections is Rs. 0.75 per mg and Rs. 1.20 per mg, respectively. For a 20 kg child the cost of therapy (6 pulses) with dexamethasone is Rs. 450 while that with methylprednisolone is Rs. 4400. The study was not funded and most patients who were randomized to methylprednisolone group were unable to afford the treatment. Only those patients who paid for the cost of methylprednisolone thus received the drug. The remaining patients were treated with dexamethasone. Finally, we had two cohorts of patients who were prospectively treated with dexamethasone and methylprednisolone over a 5-year period.

The patients were hospitalized and administered either high-dose intravenous dexamethasone or methylprednisolone at a dose of 5 mg/kg (maximum 150 mg) and 30 mg/kg (maximum 1 g) respectively. The drug was infused over a period of 2 to 3 hours, on alternate days for six doses. Oral prednisolone at a dose of 2 mg/kg was given on days when intravenous therapy was not administered. The pulse rate and blood pressure were closely monitored during the corticosteroid infusion, and patients observed for evidence of local or systemic infection.

Dipstix examination for urinary protein was done daily, and blood levels of glucose and electrolytes measured on alternate days prior to infusion. Blood levels of urea, creatinine, albumin, cholesterol and 24-hr urine albumin were measured at the initiation of therapy and at the end of six alternate-day pulses. Glomerular filtration rate was estimated from serum creatinine and height(11).

Outcome

Outcome was assessed at the end of six alternate-day pulses. Complete remission was defined as urinary protein being nil or trace on at least 3 consecutive days or urine albumin to creatinine ratio <0.2 (mg/mg). Partial remission was defined as urine protein excretion 1+ to 2+, or urine albumin to creatinine ratio between 0.2 and 2 and a serum albumin >2.5 g/dL(7). No response was defined as persistence of 3+ to 4+ proteinuria, or urine albumin to creatinine ratio >2 (nephrotic range proteinuria). Hypertension was defined as blood pressure more than the 95th percentile for the height and age(13). Outcome within the groups were compared by the Fischer's exact test with two-tail analysis or by Wilcoxon -rank sum test for numeric variables. $P < 0.05$ was taken as significant.

Results

Over the 5-year period, 59 patients with idiopathic SRNS received intravenous dexamethasone and 22 were given methylprednisolone. The baseline clinical and biochemical features of patients are shown in *Table I*. These parameters were not significantly different between dexamethasone and methylprednisolone groups.

Hypertension was seen in 31 (52.5%) patients in the dexamethasone group and 10

TABLE I–*Baseline Characteristics (median [95% CI]) of Two Groups*

	Dexamethasone group (N = 59)	Methylprednisolone group (N = 22)
Age at onset, months	29 (19.5-51.6)	33 (18-74.1)
Age at treatment, months	38 (36-92.8)	42.5 (35.5-90.4)
Boys	47	12
Systolic blood pressure, mm Hg	110 (100-116)	112 (110-120)
Diastolic blood pressure, mm Hg	70 (60-80.4)	74 (68.9-80)
Initial resistance (%)	43 (72.8)	14 (63.6)
Renal biopsy (%)		
Minimal change	21 (35.6)	5 (22.7)
FSGS	28 (47.5)	13 (59.1)
Mesangial proliferation	10 (16.9)	4 (18.2)
Blood		
Urea, mg/dL	23 (22-42.6)	30 (21.3-41.2)
Creatinine, mg/dL	0.4 (0.4-0.6)	0.5 (0.4-0.7)
Albumin, g/dL	1.8 (1.5-2.1)	1.8 (1.2-2.2)
Cholesterol, mg/dL	350 (251-488)	426 (341-494)

(47.6%) in the methylprednisolone group, prior to intravenous treatment. Of these, 22 were receiving treatment with enalapril for 4-20 weeks prior to inclusion in the study.

Three patients developed serious infections and could not complete intravenous steroid therapy (bacterial peritonitis 2, septic arthritis 1). Seventy-eight patients (dexamethasone 57, methylprednisolone 21) received the entire treatment and are included in the subsequent analyses.

At the end of the sixth alternate-day pulse, 20 (35.1%) (95% CI 22.9 - 48.9) patients in dexamethasone group and 7 (33.3%) (95% CI 14.6-56.9) patients in the methylprednisolone group were in complete remission. Seven and 3 patients each in dexamethasone and methylprednisolone group respectively, had partial remission. The median time to remission in patients who had complete remission in dexamethasone and methylprednisolone group was 9.5 and 10 days respectively. Thirty (52.6%) (95% CI 38.8 - 66.0) and 11 (52.4%) (95% CI 29.8 - 74.3) patients did not respond to intravenous dexamethasone and methylprednisolone therapy respectively. Following alternate-day pulses the median urine albumin to creatinine ratio decreased from 9.2 to 1.5 ($P < 0.005$) in dexamethasone group and from 12.1 to 0.7 ($P < 0.005$) in methylprednisolone group. The median reduction in urine albumin to creatinine ratio was 54.1 (95% CI 32.7-83.9) and 63.2 (95% CI 23.5-100) in the dexamethasone and methylprednisolone groups respectively.

Side effects

One patient each developed peritonitis and septic arthritis in dexamethasone group; one had peritonitis in methylprednisolone group. These 3 patients could not complete the treatment. Transient hypertension or worsening of preexisting hypertension was seen in 10 (47.6%) and 31 (54.3%) patients in the dexamethasone and methylprednisolone groups respectively. The hypertension was satisfactorily controlled by administration of enalapril, which was gradually withdrawn once the hypertension settled. Electrolyte abnormalities during alternate-day pulse therapy were asymptomatic and included hypokalemia (serum potassium 2.8-3.5 mEq/L) and hyponatremia (serum sodium 123-130 mEq/L) in 10 and 11 patients respectively. Hyperglycemia was seen in 2 patients in the dexamethasone group. One or more of the above side effects were observed in 66.7% (95% CI 52.9-78.6) patients treated with dexamethasone and 61.9% (95% CI 38.4-81.9) of those treated with methylprednisolone.

Discussion

High-dose intravenous corticosteroids have been widely used in various conditions where rapid anti-inflammatory or immunosuppressive action is required. While most treatment regimens comprise of methylprednisolone, intravenous dexamethasone has been used in diffuse systemic sclerosis(13), rheumatoid arthritis(14), dermatomyositis(15) systemic lupus erythematosus(16) pemphigus(17) and chronic idiopathic thrombocytopenic purpura(18). Several protocols using intravenous methyl-prednisolone and cyclophosphamide and cyclosporin A have been used in steroid resistant FSGS(3,4,7,19). Mendoza *et al.*(4) treated 32 patients of steroid resistant focal segmental glomerulosclerosis with intravenous methyl-prednisolone and alkylating agents and found a favorable response in 75% patients. Other studies using similar therapy in patients with steroid resistant FSGS showed a variable response ranging from 0-72.7% (19,20). We have previously reported our experience with

TABLE II–*Outcome after 6 Alternate-day Pulses*

	Dexamethasone (n = 57)			Methylprednisolone (n = 21)		
	Pre-treatment	Post treatment	(Confidence interval)	Pre-treatment	Post treatment	(Confidence interval)
Outcome						
Complete remission (%)	–	20 (35.1)	22.9 – 48.9	–	7 (33.3)	14.6 – 56.9
Partial remission (%)	–	7 (12.3)	5.0 – 23.7	–	3 (14.3)	3.0 – 36.3
No response (%)	57 (100%)	30 (52.6)	38.9 – 66.0	21 (100%)	11 (52.4)	29.9 – 74.3
Proteinuria (g/24h)**	1.9	0.7		2.2	0.2	–
UaUc (mg/mg)**	9.2*	1.5*		12.1#	0.7#	
Percentage reduction in UaUc ratio**	–	54.1	32.7 – 83.9	–	63	23.5 – 100
Side effects						
Transient hypertension	–	54.4%	40.7 – 67.7	–	47.6%	25.7 – 70.2
Any side effect		66.7%	52.9 – 78.6		61.9%	38.4 – 81.9

*# P value <0.005; **median values UaUc = Urine albumin to creatinine ratio

a modified protocol chiefly using intravenous dexamethasone. Complete remission was achieved in 28.8% and partial remission in 13% subjects(9). There are however no previous reports on the use of intravenous dexamethasone as an immunosuppressive agent in the treatment of glomerular diseases.

Methylprednisolone results from methylation at 6-a position of prednisolone, while dexamethasone is produced by methylation at l6-a position of 9-fluroprednisolone. These synthetic corticosteroids in contrast to natural steroids, have potent glucocorticoid action and minimal mineralocorticoid activity. Dexamethasone has more potent anti-inflammatory activity than methylprednisolone, because of its increased affinity for glucocorticoid receptors and less protein binding(21). It also has longer half-life than methylprednisolone due to its decreased hepatic metabolism. The prolonged half-life of dexamethasone may produce greater degree of hypothalamic-pituitary axis suppression and thus prolonged immunosuppression as compared to methylprednisolone(21). However. methylprednisolone may have an advantage over dexamethasone as it penetrates the cell membrane more quickly than dexamethasone(22).

There are few studies comparing the efficacy of high-dose dexamethasone and methylprednisolone in non-renal disorders. Dexamethasone has significantly less mineralocorticoid activity than methylprednisolone and is preferred for treatment of cerebral edema. However Quandt, *et al.*(23) found no difference between the efficacy of these drugs for the treatment of cerebral edema in patients with head injury. In a prospective study in patients with septic shock, 30 mg/kg of methylprednisolone and 6 mg/kg of dexamethasone were found to be similar in efficacy in reducing mortality, with no difference in side effects(24). Lashina, *et al.*(14) compared the efficacy of intravenous dexamethasone (2 mg/kg) and methylprednisolone (l g) for the treatment of rheumatoid arthritis in adults. Both drugs were found to be equally efficacious in reducing the severity of arthralgia, morning stiffness and number of inflamed joints one month after the treatment(14). Similarly, in a prospective randomized trial, there was no difference in the visual acuity after administration of intravenous dexamethasone or methylprednisolone for traumatic optic atrophy(25).

In the present study, two cohorts of patients with SRNS were simultaneously treated with intravenous dexamethasone or methylprednisolone for two weeks and their short-term effect on the course of SRNS was studied. Due to cost constraints we treated more patients with dexamethasone than methylprednisolone. The baseline characteristics of the treatment groups were not different. However, the selection of patients was determined by the ability of their family to afford a particular drug and could have been a source of bias. The socioeconomic status of patients receiving dexamethasone and methyl-prednisolone was also likely to be different.

In view of the likely selection bias, we have not tried to statistically compare the rate of remission in between the treatment groups. The 95% confidence interval of the proportion of patients achieving complete remission in the dexamethasone group was 22.9-48.9 and in methylprednisolone group 14.6-56.9. These were not different suggesting that high-dose intravenous dexamethasone and methyl-prednisolone may be equally efficacious in inducing remission in SRNS. There was also no difference in the short -term side effects of these drugs. Twenty seven percent patients in this study were receiving enalapril. The

Key Messages

- High-dose intravenous dexamethasone is as effective as methylprednisolone in inducing remission in steroid resistant nephrotic syndrome.
- Dexamethasone may be used as an alternative to methylprednisolone.

possibility that enalapril could have caused a significant reduction in proteinuria in these patients is unlikely because the drug was being used in these patients for at least 4 weeks before starting intravenous corticosteroids. Moreover the observed reduction in proteinuria occurred following a short period of therapy with intravenous corticosteroids.

Results from this study suggest that two weeks treatment with high-dose intravenous dexamethasone seems to be as efficacious as methylprednisolone in inducing remission in SRNS. However, long-term benefits of treatment with these drugs in the form of sustained remission of proteinuria and prevention of renal insufficiency are unclear, as these were not studied. Although there is a need to conduct a randomized controlled trial to compare the short as well as long-term clinical efficacy and cost effectiveness of these drugs, we believe that intravenous dexamethasone can be used as an alternative for the treatment of patients with SRNS.

Contributors: PH, AB and MM managed the patients and collected the data; PH drafted the manuscript; AB reviewed the manuscript and will act as its guarantor.

Funding: None.

Competing interests: None stated.

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