EARLY HIGH-DOSE ORAL CORTICOSTEROIDS AND AVASCULAR HIP NECROSIS IN RENAL TRANSPLANTS

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SYNOPSIS

Cumulative doses of oral and intravenous (i.v.) corticosteroids during the 1st 12 months (mos) after grafting were assessed in 26 renal-graft recipients with avascular hip necrosis (AHN) and 28 controls without AHN who were matched for sex, age, type of graft, time of grafting and duration of follow-up.

AHN recipients had significantly higher cumulative doses of oral predvisolone (PNL) (1.705 +/− 0.283 vs 1.515 +/− 0.275 Gm, $p < 0.05$; 4.013 +/− 0.893 vs 3.561 +/− 0.654 Gm, $p < 0.04$) at 1 and 3 mos respectively post-grafting as compared to the control. However, the two groups did not differ significantly in cumulative doses of i.v. hydrocortisone (3.873 +/− 2.119 vs 3.021 +/− 0.756 Gm, $p > 0.05$) at 3 most, i.v. methyl prednisolone (1.107 +/− 1.912 vs 1.446 +/2.327 Gm, $p = 0.56$) at 3 mos and oral and i.v. corticosteroids at 12 mos.

Our findings suggest that high-dose oral PNL during the early post-grafting period may be associated with a higher prevalence of AHN in renal-graft recipients.

INTRODUCTION

Avascular hip necrosis (AHN) has been a recognised complication of transplant surgery. (1) The prevalence of AHN varies from 3% (8) to 40% (10) following organ grafting. Corticosteroids appears to be related to the development of AHN. (2, 3, 4) However, the contribution of high dose corticosteroids to AHN has been shown only in some studies (5, 6, 7) but not in others. (2, 8, 9, 10)

The purpose of this paper is to determine if renal graft recipients with AHN had higher cumulative doses of corticosteroids during the early period after grafting.

METHODS & MATERIALS

From 1970 to 1984, 186 renal transplantation (107 living-related donor, 79 cadaveric donor) were performed on 184 non-diabetic recipients in Singapore General Hospital. One hundred and twenty-one (68 males, 53 females) of these recipients were followed up for 1 to 14.5 years (mean, 3.8 years). Their ages ranged from 15 to 53 years (mean, 29.3 years).

Immunosuppression consisted of corticosteroids and azathiaprine. Intravenous hydrocortisone (IV HDC) 1 Gm was given on the day of and two subsequent days after grafting. Thereafter, oral prednisolone (PNL) 100 mg/day was given and reduced subsequently by 5 mg per day until 60 mg/day was reached. The latter dosage was further reduced by 5 mg/week until 30 mg/day. Nine months after grafting, most patients reached the maintenance dose of 10 mg/day. Since mid-1983, the starting dosage of PNL has been reduced to 60 mg/day. By the end of 3 months, the dosage has come down to 20 mg/day. The maintenance dose of 10 mg/day was achieved by 6 months after grafting. The azathinaprine dose was 1.5 mg/kg/day to 2 mg/kg/day. Acute rejection was treated with three doses of either intravenous methylprednisolone (IV MPNL) 0.5 — 1.0 Gm or IV HDC 1 Gm over three days.

The diagnosis of AHN was confirmed by radiological examination of the hip. This investigation was only performed on symptomatic patients who either complained of hip and/or knee pains or reduced mobility of the hip joint. For the purpose of comparison, a control group of patients matched for age, sex, type of graft, time of grafting and duration of follow-up was selected for the patients with AHN.

Cumulative doses of IV HDC, IV MPNL and oral PNL were calculated separately for the 1st month, 3 months and 12 months after grafting in both groups. Values are expressed as mean ±/− SD. Differences between the two groups were analysed using paired Student's t test.

RESULTS

Out of 121 graft recipients, 28 (23%) who had been observed for 1 to 14.9 years (mean, 5.1 years) developed AHN. Fifteen of them were males and 13 were females. Their ages ranged from 16 to 40 years (mean, 31 years). Twenty of the grafts were living-related donor and the remaining 8 were cadaveric. The time of onset of AHN was 4 to 37 months (mean, 13.6 months) after grafting.

The 12-month cumulative doses of corticosteroids (IV HDC, 4.436 +/−2.836 vs 3.509+/−1.581 Gm, $p>0.14$; IV MPNL, 1.679+/−2.345 vs 2.625+/−3.205 Gm, $p>0.22$; oral PNL, 8.851+/−2.248 vs 8.440 +/−1.162 Gm, $p>0.45$) did not differ significantly between the AHN and the control groups (Table 1). In addition, the number of rejection episodes in both groups were comparable i.e. one episode per patient per year.

However, the AHN group has significantly higher cumulative doses of oral PNL (1.705+/−0.283 vs 1.515+/−0.275 Gm, $p<0.05$; 4.013+/−0.893 vs 3.561+/−0.654 Gm, $p<0.04$) at 1 and 3 months respectively after grafting as compared to the control (Table 1). The doses of oral PNL administered between the time of grafting and the onset of AHN varied from 4.439 to 21.181 Gm (mean, 9.120 Gm). In contrast, the AHN and the control groups did not differ significantly in cumulative doses of IV HDC (3.873+/−2.119 vs 3.021+

TABLE 1

	AHN Group	Control Group	'P' Value**
No of patients	28	28	
Sex (F/M)	13/15	13/15	
Age (yrs)*	30.6+/−6.2	29.9+/−6.8	NS
Type of graft (LRD/CD)#	20/8	20/8	
Duration of follow-up (yrs)*	5.0+/−3.1	4.5+/−8.2	NS
Cumulative doses of oral PNL (Gm)*			
1 month	1.705+/−0.283	1.515−/−0.275	<0.05
3 months	4.013+/−9.893	3.561+/−0.654	<0.05
12 months	8.851+/−2.248	8.440+/−1.162	NS
Cumulative doses of IV HDC (Gm)*			
3 months	3.873+/−2.119	3.021+/−0.756	NS
12 months	4.436+/−2.836	3.509+/−1.581	NS
Cumulative doses of IV MPNL (Gm)*			
3 months	1.107+/−1.912	1.446+/−3.327	NS
12 months	1.679+/−2.435	2.625+/−3.205	NS

* Value expressed as mean +/− SD

\# LRD — living-related donor
CD — cadaveric donor

** NS denotes not significant

/ – 0.756 Gm; p>0.05) and IV MPNL (1.107 + / – 1.912 vs 1.446 + / – 2.327, p = 0.56) during the first 3 months (Table 1).

DISCUSSION

The role of corticosteroids in the causation of osteonecrosis has been suggested by many studies (11). In organ grafting, approximately 16% (9) of recipients develop osteonecrosis) and the hip joint is most commonly involved. Fifteen percent of our renal graft recipients developed AHN. For those who had been observed for at least 1 years, 23% developed AHN within a mean period of 13.6 months after grafting. The true incidence may have been higher as routine radiological examination of the hip was not carried on our recipients.

Whether intravenous high-dose corticosteroids used for treating acute rejection are more likely to result in AHN is still uncertain (2, 5, 6, 7, 8, 9, 10). One recent report (12) indicated a significant correlation between the number of IV MPNL pulses and occurrence of AHN. Our results failed to show any significant difference in the cumulative doses of IV HDC or IV MPNL at 3 and 12 months after grafting between the AHN and the control groups. In addition, both groups had the same number of rejection episodes. It is of interest to note that our recipients had relatively low cumulative doses of intravenous corticosteroids and fewer rejection episodes. These factor might have some bearing on the negative influence of IV HDC and IV MPNL on the occurrence of AHN.

However, our AHN recipients had significantly higher cumulative doses of oral PNL during the first and 3 months but not 12 months post-grafting as compared to the control group. These findings are in agreement with a previous report (19) that showed a significant correlation between mean daily corticosteroid dose during the first post-grafting month and the occurrence of avascular osteonecrosis. It appears that low dose PNL during the early post-grafting period may be crucial in avoiding the onset of AHN. This is supported by the impressively low incidence of AHN in recipients treated with low dose PNL regime. (13)

Although AHN in organ grafting is largely attributable to corticosteroids, the precise mechanisms of injury to the bone are unclear. Various hypotheses have been postulated and these include fat embolism, (14) osteoporosis, (15) coagulation abnormalities, (16) increased intraosseous pressure (17) and fat cell swelling. (18) There are currently no markers predictive of the development of AHN in transplant recipients. Factors such as body weight, pre-existing bone disease and duration of haemodialysis prior to grafting which may be of importance in the pathogenesis of AHN were not examined in our study.

In conclusion, we have found a significantly higher cumulative doses of oral PNL received by renal graft recipients with AHN at 1 and 3 but not 12 months post-grafting as compared to the control group. However, the 3- and 12-month cumulative doses of IV HDC and IV MPNL were not significantly higher in the AHN recipients. Our findings suggest that high dose oral PNL during the early post-grafting period may be associated with a higher prevalence of AHN in renal-graft recipients.

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