PAPERS AND SHORT REPORTS

High versus "low" dose corticosteroids in recipients of cadaveric kidneys: prospective controlled trial

J PAPADAKIS, C B BROWN, J S CAMERON, D ADU, M BEWICK, R DONAGHEY, C S OGG, C RUDGE, D G WILLIAMS, D TAUBE

Abstract

Corticosteroids have the major role in the immunosuppressive treatment of patients who have received renal transplants. Despite their extensive use there is still debate about the appropriate dose that will prevent rejection of the renal allograft with the least morbidity. From March 1979 to November 1981 a randomised controlled trial of high (33 patients) v low oral dose (34 patients) of prednisolone along with azathioprine was conducted in recipients of first cadaveric transplants who had received a blood transfusion within six months of transplantation. The main difference in outcome between the two groups was a high incidence of some infections in the high dose group. Patient mortality, graft survival, transplant function, and number of rejection episodes were indistinguishable in the two groups, but rejection episodes tended to occur later in the high dose group.

These findings suggest that the use of lower doses of corticosteroids soon after cadaveric renal transplantation does not jeopardise graft survival and results in lower patient morbidity.

Guy's Hospital, London SE1 9RT

J PAPADAKIS, MD, honorary senior registrar
C B BROWN, BSC, MRCP, senior registrar
J S CAMERON, MD, FRCP, professor of renal medicine
D ADU, MD, MRCP, senior registrar
M BEWICK, MCH, FRCS, consultant transplant surgeon
R DONAGHEY, SRN, transplant sister
C S OGG, MD, FRCP, director, renal and transplant unit
C RUDGE, MB, FRCS, consultant transplant surgeon
D G WILLIAMS, MD, FRCP, consultant renal physician
D TAUBE, BM, MRCP, senior registrar

Correspondence to: Professor J S Cameron, Clinical Science Laboratories, 17th Floor Guy's Tower, Guy's Hospital, London SE1 9RT.

Introduction

Since 1963, when Goodwin *et al* reported the use of corticosteroids in the immunosuppressive treatment after human renal transplantation,[1] corticosteroids and azathioprine have been the main chemical immunosuppressive agents used in recipients of renal transplants. Despite extensive use of corticosteroids, the optimal dose for the prevention of graft rejection with the least side effects has not been established. High doses of steroids are still used in several units in the early months after transplantation before maintenance doses of 10-20 mg/24 h are established. On the other hand, the use of low dose steroids from the outset has been supported strongly by the excellent results of McGeown *et al*[2-4] who used 20 mg of prednisolone from the day after transplantation. This is reinforced by the findings of Kreis *et al*, who avoided the use of steroids altogether immediately after transplantation, and believed that in the absence of obvious rejection some patients may not need corticosteroids at all.[5] Recently Buckels *et al*[6] and Morris *et al*,[7] in prospective trials in recipients of cadaveric kidneys, compared the use of high dose and low dose steroids and reported that the use of low doses of prednisolone from the day after transplantation does not jeopardise graft survival and results in lower morbidity.

We conducted a prospective trial of high versus low dose corticosteroids in patients receiving first cadaveric transplants. Our purpose was to see if there were differences between the two regimens in their ability to prevent rejection, and in the mortality and morbidity which they induced in patients who had received renal transplants.

Patients and methods

PATIENTS

From March 1979 to November 1981 all patients who were to receive first cadaveric allografted kidneys were entered into the trial: no patients were excluded. Thus a total of 67 patients, all aged over 15 years, were studied. All had received a standard transfusion (5 units of blood from a donor that was more than 10 days old and had been chosen at random) within six months of transplantation.

Patients were allocated at random to receive high or low doses of corticosteroids. A series of sealed envelopes, in random order but

stratified beforehand to ensure that each group of 10 consecutive envelopes contained five allocations to each group, was used for randomisation. The envelopes were taken consecutively for each new patient.

Seven patients had to be withdrawn from the trial for various reasons (see table I); their data were used up to the date of withdrawal.

TABLE I—*Details of patients withdrawn from trial*

Sex	Age	Time in trial (weeks)*	Reason for withdrawal
			High dose
M	57	4	Decrease of steroids—wound infection
M	47	4	Decrease of steroids—wound infection
F	35	3	Decrease of steroids—endocarditis
M	49	20	Increase of steroids—phenytoin administration
M	18	10	Increase of steroids—thrombocytopenia
			Low dose
F	25	6	Increase of steroids—phenytoin administration
M	57	15	Increase of steroids—prolonged poor transplant function

* Data for this period *included* in analysis of two groups.

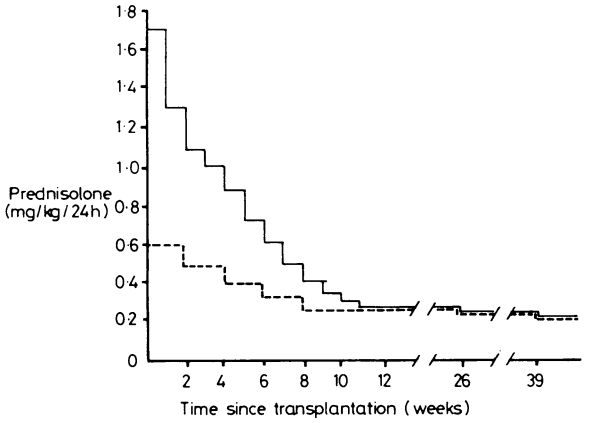

FIG 1—Dose of prednisolone given during first year after transplantation in patients receiving high (—) and low (- - -) dose corticosteroids.

TRIAL DESIGN

The question asked was whether a reduction in the early high dosage of prednisolone during the first three months would lead to an increased loss of grafts; the possibility that reduction might lead to better results was recognised, but our principal anxiety was to establish if there was any deterioration in results. We calculated that a study of 70 patients would allow us a 1 in 20 chance of determining whether the results had deteriorated by 20%, this being judged as an unacceptable level of deterioration. In this calculation it was assumed that survival rate of first cadaveric grafts in the group receiving the high dose would be 60% after two years.

The high dose regimen was that in standard use in the transplant unit for a decade; the low dose regimen was the regimen, admittedly arbitrary, which was the lowest acceptable to all the clinicians in the unit. Since the steroid dosage was given according to bodyweight (see below) we planned that the heavier patients would receive rather more during the first three months than the dose described by McGeown and colleagues,[2] while the lighter patients would receive less. We did not, however, use the prolonged high dose regimen for acute rejection episodes as described from Belfast.[2]

Figure 1 shows the schedule of steroids that was given to the patients: 33 patients received the high dose and 34 the low dose. The daily dose of corticosteroids was given in two divided doses, the evening dose gradually being phased out as dosage was reduced. All patients also received azathioprine, 2·5 mg/kg/day, which was omitted temporarily in the presence of leucopenia (< 5000 white blood cells/μl). Acute rejection episodes were treated in both groups with 1 g methylprednisolone given intravenously on three consecutive days.

ANALYSIS OF OUTCOME

The two groups were compared for factors that could influence graft survival—sex, age, primary renal disease, HLA-A and HLA-B mismatches, blood group, and parity. All patients had received at least 5 units of 10 day old blood before transplantation. Patient mortality, graft survival, renal function as estimated by the plasma creatinine concentration (μmol/l), the number of rejection episodes, and the day of onset of the first rejection episodes were compared in the two groups.

ANALYSIS OF COMPLICATIONS

The incidence of infections, which were divided into urinary tract infections, chest infections, and "others" was analysed. Other infections included wound infection; bacterial infections in sites apart from the urinary tract, the lung, and the wound; positive blood cultures; cytomegalovirus infections; herpes virus infections; and pyrexia of undetermined origin. We also recorded the incidence of other complications that might be attributed to corticosteroids, such as avascular necrosis of bone, alimentary tract complications, steroid induced diabetes, and cataracts. Finally, the rate of healing of the transplant wound and the duration of hospital admission during and after transplantation were compared.

STATISTICAL METHODS

The life table method[8] was used to analyse the survival of grafts and of patients, the time to first rejection, and the time to discharge from hospital. The Cox-Mantel logrank test was used to test the differences. The χ^2 method was used to assess possible differences in the composition of the two groups, the infection rates and possible steroid related complications. Student's t test was used to test the differences in ages of the two groups, the total number of rejection episodes, and the number of episodes in the first month, and the plasma creatinine concentrations in surviving grafts.

Results

There was no difference between the groups ($p < 0·05$) in all factors believed to influence graft survival (table II).

TABLE II—*Details of factors that might influence graft survival. Figures are numbers (%) of patients*

	High dose (n = 33)	Low dose (n = 34)
Men	21	24
Women	12	10
Age (years)	42·0 ± 15·4 (SD)	44·4 ± 15·4 (SD)
Primary renal disease:		
Glomerulonephritis	8 (25)	13 (38)
Reflux/pyelonephritis	3 (9)	2 (6)
Polycystic kidneys	6 (18)	7 (20)
Hypertension	1 (3)	6 (18)
Hereditary disease	5 (15)	1 (3)
Others	10 (30)	5 (15)
HLA-A and HLA-B mismatches		
4 mismatches	14 (42)	8 (24)
3 mismatches	11 (33)	12 (35)
2,1 mismatches	8 (25)	14 (41)
Blood group:		
O	10 (30)	14 (41)
A	18 (54)	15 (44)
B, AB	5 (16)	5 (15)
Parity:		
Multiparous	6 (50)	6 (60)
Nulliparous	6 (50)	4 (40)

DEATHS

One patient out of the 33 who had received a high dose died from faecal peritonitis after a perforated ischaemic colon; his graft had been placed successfully on a Dacron iliac bypass graft, but intestinal circulation became insufficient. Three patients out of the 34 who had received a low dose died: one from a myocardial infarct in a hypotensive episode, itself following a bleed from the renal anastomosis during anticoagulation for a postoperative deep venous thrombosis; another from rupture of a known aneurysm while waiting for replacement 15 months after transplant; and a third from a cerebrovascular accident. The last two of these three patients had functioning grafts.

One other patient, in the high dose group, died (after graft failure) of a myocardial infarct one and a half months after returning to haemodialysis treatment; he has not been included in the calculation of patient survival in fig 2, but as a death on haemodialysis. The youngest of the patients who died was 49 years; none of the others were under the age of 50.

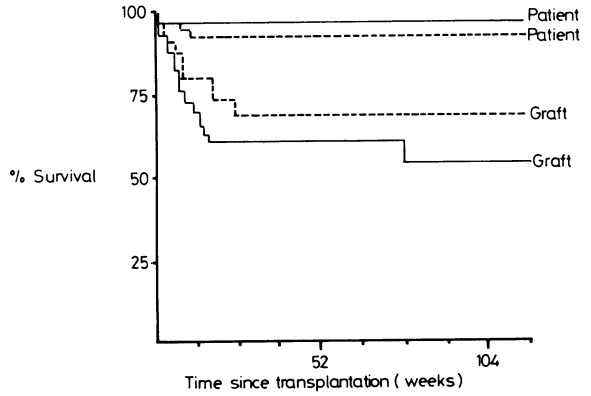

FIG 2—Life table analysis of survival of patient and graft in those receiving high (——) and low dose (- - - -). Data from patients who were withdrawn from the trial (see text) were used up to point of withdrawal, and deaths of patients with functioning graft were noted as cessation of follow up in calculating graft survival.

GRAFT SURVIVAL AND FUNCTION

Thirteen grafts of the 33 were lost in the high dose group and 10 of the 34 in the low dose group. Survival rates calculated actuarially at two years were 55% for the high dose group and 68% for the low dose group (fig 2). There was no difference between these two sets of data on logrank testing ($p = 0{\cdot}12$), and a less than 0·05 chance that these data are compatible with a true reduction in graft survival of 20% ($\chi^2 = 3{\cdot}88$), the initial target of the trial. There is, however, a 1 in 5 chance that a smaller reduction in graft survival might occur at the 10% level, and this possibility is not excluded by our data because of the small numbers entered.

In the life table analysis the grafts of the patients who died with functioning grafts, as well as those of the patients who were withdrawn from the trial, were considered as functioning grafts with duration of function equal to the time that they were followed up in the trial.

There was no difference between the groups in the renal function of the patients with functioning grafts, as shown by plasma creatinine concentrations (fig 3).

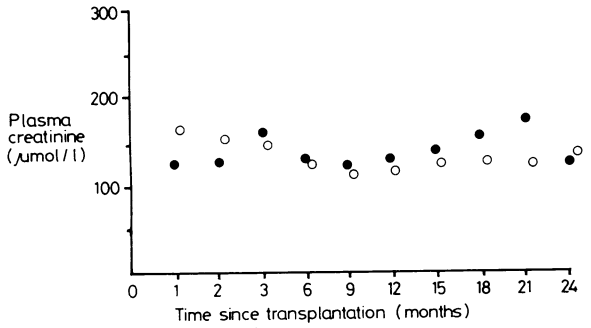

FIG 3—Mean plasma creatinine concentrations (±1SD) in patients with functioning grafts; (patients in high (●) and low (○) dose groups). None of means are different at 0·05 level. *Conversion: SI to traditional units*—Creatinine 1 μmol/l ≈ 0·01 mg/100 ml.

REJECTION EPISODES

There was no difference between the two groups in the total number of rejection episodes or in the number of rejection episodes occurring during the first three months after transplantation. There was, however, a significant difference in the time to first rejection episodes ($p < 0{\cdot}05$) and in number of rejection episodes during the first month after transplantation, during which period more rejection episodes were diagnosed in the low dose group ($p = 0{\cdot}05$) (table III).

TABLE III—*No and timing of rejection episodes in patients receiving high or low dose. Results are means ±1SD*

	High dose	Low dose	p Value
Rejection episodes:			
Total	3·36 ± 2·23	3·55 ± 1·90	NS
No occurring in first three months	2·60 ± 1·51	3·02 ± 1·38	NS
No occurring in first month	1·72 ± 0·91	2·17 ± 0·96	= 0·05
Day of first rejection episode (after operation)	6·72 ± 4·88	8·23 ± 4·64	NS

NS = Not significant.

COMPLICATIONS

Infections were the most frequent complication in both groups, although no patient died of it. There was no significant difference in the number of patients who presented with urinary tract infections or chest infections, although their incidence was greater in the patients receiving high dose. A significant difference was found in the number of patients in the high dose group with "other" infections (table VI); table V shows the actual numbers and types of these infections, with a higher incidence of almost all types of infection in the high dose group.

The incidence of other complications that might be attributed to corticosteroids was not significantly different in the two groups, although their incidence was greater in the higher dose group (table VI).

Wound healing and admission to hospital—By 15 days after operation, 21 wounds had healed in the high dose group and 30 in the low dose group ($p < 0{\cdot}05$). No significant difference was found in the time that the patients in the two groups spent in hospital during and after the transplantation (fig 4) by the logrank analysis ($p > 0{\cdot}10$) although the six patients with the longest stay were all receiving the high dosage regimen.

TABLE IV—*No of patients in each group with different types of infections*

	High dose (n = 33)	Low dose (n = 34)	p Value
Urinary tract infection:			
Men	9	7	
Women	7	4	NS
Total	16	11	
Chest infection	11	9	NS
Other infections	29	11	<0·001

NS = Not significant.

TABLE V—*Details of episodes of infections outside respiratory and urinary tracts*

	High*	Low*
Wound	10	3
Other sites	9	3
Positive blood culture	6	2
Cytomegalovirus infection	7	1
Herpes simplex virus infection	7	3
Pyrexia of undetermined origin	1	1
Total	40	13

* High dose group = 29 patients, low dose group = 11 patients.

TABLE VI—*No of patients who presented with complications that might be attributed to steroid treatment*

	High dose	Low dose
Avascular necrosis of bone	2	0
Gastrointestinal bleeding and/or ulcers*	2	4
Gastritis or oesophagitis* (endoscopic diagnosis)	0	2
Perforation of gut	4	0
Diabetes mellitus	2	4
Cataract	3	0
Deep vein thrombosis	3	2
Total	16	12

* Six patients receiving high dose and seven receiving low dose were treated with cimetidine.

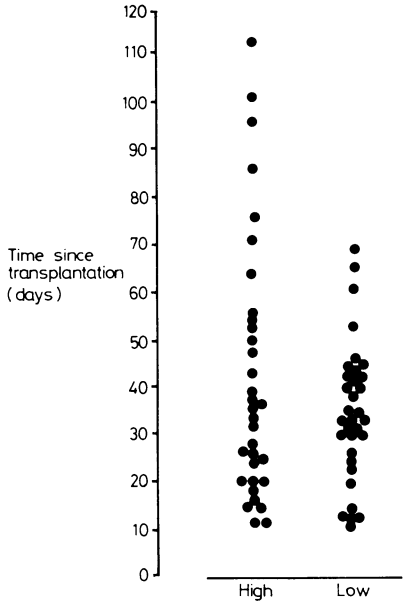

FIG 4—Day of discharge from hospital in two groups of patients. No difference by the logrank method between two sets of data.

Discussion

Renal transplantation has become the treatment of choice in end stage renal failure as it has led to excellent rehabilitation of patients[9] and is cheaper than dialysis.[10] The problems of morbidity and graft failure, however, have by no means been resolved. A "safe" immunosuppressive regimen would probably be the key to their solution. This, for the present, means the optimal use of azathioprine and corticosteroids, although the impact of cyclosporin[11] may yet be considerable. Debate concerning the optimum dose of corticosteroids continues, and many units follow the policy that "more is best," although several reports—including our own—support the idea that lower doses are equally effective.[2-4 6 7]

Our trial was conducted at about the same time as the trials in Birmingham[6] and Oxford,[7] but in some ways is superior in design. Our corticosteroid dose was based on bodyweight, all the patients were receiving first cadaveric transplants, and all had received transfusions before transplantation. In the Birmingham trial the doses of corticosteroids were fixed, so that the corticosteroid activity could be influenced by the patient's bodyweight. Not all their patients had had transfusions, and some had received more than one allograft. In the Oxford trial the doses of corticosteroids were also fixed, and the patients in the low dose group routinely received 1 g of intravenous methylprednisolone on the sixth, seventh, and eighth day after transplantation, and the gap between the two regimens may have been decreased by this. Some of their patients had received more than one allograft, and only 60% of them had had transfusions before transplantation. Our rate of survival for patients and grafts is, however, similar to those of the other two groups, and not different to those of other units.[2 3 7] This must be seen in relation to the fact that our patients were older—about half were over 45 and a quarter over 60—and that all patients received the same corticosteroid dosage from 12 weeks onwards.

The analysis of graft survival and the study of renal function showed that the low doses of corticosteroids used appear to cover the patients from the danger of loss of function in their grafts to the same extent as higher initial doses. In fact, the results were better in the low dose group, though not statistically significant. Because of small numbers, our data cannot exclude the possibility of a smaller reduction in graft survival at the 10% level,[12] although we have excluded the possibility of a 20% reduction. Four deaths were asymmetrically distributed, three being in the low and one in the high dose group, but again this does not reach significance; examination of the circumstances of death suggests that at least two were coincidental and unrelated to treatment. The zero mortality in patients under the age of 45 was gratifying. The number of acute rejection episodes was indistinguishable between the two groups, but the time to first rejection was longer and the number of rejection episodes in the first month lower in the high dose group. This postponement of early rejection did not seem to affect long term survival of the grafts.

Both bacterial and viral infections outside the respiratory and urinary tracts were more common in the high dose group. It is accepted that there is a direct relation between the incidence of infection and the quantity of immunosuppressive treatment in patients who have received renal transplants.[10 13] Because the rest of the immunosuppressive treatment was the same in the two groups, the greater incidence of almost all the infections in the patients in the high dose group must be attributed to the higher dose of corticosteroids that was given to them.

The morbidity from the other complications that may be attributed to corticosteroids was not different in the two groups, although it is noteworthy that again more patients in the high dose group were affected by them. Analysis of the number of transplant incisions healed within 15 days of transplantation showed that wounds of the patients in the high dose group needed longer to heal. This may be partially due to the increased incidence of wound infections in the high dose group, because most wound infections were infections of the transplant incision. We cannot, however, exclude a direct influence of corticosteroids in this prolongation of the time to healing, a fact which contributes to the patients' morbidity.

Our results clearly show that low doses of corticosteroids, with azathioprine, were not only sufficient as immunosuppressive treatment but they also led to less morbidity in the patients. Since this trial has finished, we have continued the low dose regimen in all our patients receiving renal transplants. To determine whether even lower doses of corticosteroids could be used with even greater safety and comparable (or better) results will require a further trial.

References

1 Goodwin WE, Kaufman JJ, Mims MM, *et al.* Human renal transplantation. I. Clinical experiences with six cases of renal hormotransplantation. *J Urol* 1963;**89**:13-24.

2 McGeown MG, Loughridge WGG, Alexander JA, *et al.* One hundred kidney transplants in the Belfast City Hospital. *Lancet* 1977;ii:648-51.

3 McGeown MG, Douglas JF, Brown WA, *et al.* Low dose steroids from the day following renal transplantation. *Proc Eur Dial Transplant Assoc* 1979;**16**:395-9.

4 McGeown MG, Douglas JF, Brown WA, *et al.* Advantages of low dose steroids from the day after renal transplantation. *Transplantation* 1980; **29**:278-9.

5 Kreis H, Noel LH, Chailley J, Lacombe M, Descamps JM, Crosnier J. Kidney graft rejection: has the need for steroids to be re-evaluated? *Lancet* 1978;ii:1169-72.

6 Buckels JAC, Mackintosh P, Barnes AD. Controlled trial of low versus high dose oral steroids therapy in 100 cadaveric renal transplants. *Proc Eur Dial Transplant Assoc* 1980;**18**:394-8.

7 Morris PJ, French ME, Chan L, Ting A. Low dose oral prednisolone in renal transplantation. *Lancet* 1982;ii:525-7.

8 Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977;**35**:1-39.

9 Morris PJ. Results of renal transplantation. In: Morris PJ, ed. *Kidney transplantation: principles and practice.* London: Academic Press, 1979: 377-88.

10 Guttman RD. Renal transplantation (second of two parts). *N Engl J Med* 1979;**301**:1038-48.

11 European Multicentre Trial. Preliminary results. Cyclosporin A as sole immunosuppressive agent in recipients of kidney allografts from cadaver donors. *Lancet* 1982;ii:57-60.

12 Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the *randomised control* trial. Survey of 71 "negative" trials. *N Engl J Med* 1978;**299**:260-4.

13 Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE. Infection in the renal transplant recipient. *Am J Med* 1981;**70**:405-11.

(*Accepted 3 February 1983*)