

Corticosteroid administration within 2 weeks after renal transplantation affects the incidence of femoral head osteonecrosis

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Background and purpose — It has been suggested that avascular osteonecrosis (AVN) of the femoral head occurs early after systemic steroid administration. The purpose of this study was to investigate the risks regarding development of AVN at a very early stage after renal transplantation.

Methods — The presence or absence of AVN was determined by MRI at 4 weeks, at 6–12 weeks, at 24 weeks, and at 12 months after renal transplantation in 286 patients (183 males) with a mean age of 39 (16–65) years. The relationship between AVN and age, sex, absence or presence of acute rejection (AR), type of transplanted kidney (living or cadaveric), type of immune suppressor, and total dose of orally administered steroids given in the 2-week period after transplantation was investigated.

Results — There were no statistically significant correlations between the development of AVN and age, sex, absence or presence of AR, type of transplanted kidney, or type of immune suppressor. A significant dose-response relationship was found between development of AVN and the total dose of steroid administered in the first 2 weeks after surgery.

Interpretation — We found a relationship between AVN development and steroid dose in the early postoperative period, and we also showed a dose-response relationship.

contribute to the development of AVN. In addition, it has been reported that the incidence of acute rejection (AR) after renal transplantation is related to AVN development (Harrington et al. 1971, Tang et al. 2000). Development of AVN was found to be less frequent in a group that received tacrolimus than in a group that received cyclosporine (Sakai et al. 2003, Abbott et al. 2005).

In patients who have undergone renal transplantation, T1-weighted MRI shows a band pattern in the femoral head at around 6–12 weeks postoperatively (Kubo et al. 1997, Fujioka et al. 2001). This indicates that AVN occurs very early after renal transplantation. MRI has been reported to have high sensitivity and specificity for the diagnosis of AVN (Sugano et al. 1999), and should be used for precise assessment of AVN development. Only a few reports have used MRI to determine the risk of AVN development in the early period after renal transplantation; this includes studies that have shown statistically significant relationships (1) between AVN development and total dose of steroid within 2 months postoperatively (Shibatani et al. 2008), and (2) between AVN development and delayed renal function (Takao et al. 2011).

We wanted to determine the risks regarding development of femoral head AVN at an earlier stage than those evaluated in previous studies after renal transplantation.

Avascular osteonecrosis (AVN) of the femoral head is one of the major complications of renal transplantation. It is known to develop in the early postoperative phase in 3–40% of patients (Hawkins et al. 1974, Pierides et al. 1975, Tuncay et al. 1998, Veenstra et al. 1999, Takao et al. 2011). The total steroid dose within 3 weeks postoperatively (Harrington et al. 1971), the total dose within 3 months postoperatively (Pierides et al. 1975), the total dose within the first year postoperatively, and the average daily dose (Tang et al. 2000) have been reported to

Patients and methods

Study design

Between January 1988 and December 2007, 424 patients underwent renal transplantation at the Department of Transplantation and Endocrine Surgery, Kyoto Prefectural University of Medicine. Of these, 297 patients were eligible for MRI screening. After excluding patients aged 15 years or younger,

286 patients (183 males) with a mean age of 39 (16–65) years were included in this study; 189 patients received cyclosporine and 97 patients received tacrolimus.

Routine MRI of the hips was done preoperatively (or at 4 weeks), at 6–12 weeks, at 24 weeks, and at 12 months after transplantation. MRI was performed as previously described (Kubo et al. 1997, Fujioka et al. 2001) using a 0.5-tesla superconducting magnet (in the period 1988–1990) or a 1.5-tesla superconducting magnet (in the period 1990–2008). T1-weighted images, T2-weighted images, and fat suppression images (short TI inversion recovery, STIR) on the coronal plane were obtained. The slice thickness was 5 mm. The presence or absence of AVN was determined based on the criteria of Sugano et al. (1999). A low-intensity band on T1-weighted images (band pattern) separating the normal fat intensity area in MRI was classified as AVN. The patients who had abnormal patterns in MRI underwent conventional radiography and bone scan of the hips. The patient information collected included age, sex, absence or presence of AR, type of transplanted kidney (living or cadaveric), type of immune suppressor used (cyclosporine or tacrolimus), and total dose of orally administered steroids given in the 2-week period after transplantation. Approval for this study is being applied for at the institutional review board of our institution.

Administration of steroid

In all patients, methylprednisolone (MPSL; 500 mg) was administered intravenously during surgery and prednisolone (PSL; 50 mg intravenously) was administered immediately after surgery. Oral PSL administration was started on postoperative day (PD) 1. Three oral PSL administration schedules were employed during the first 2 weeks postoperatively. Cases undergoing surgery from January 1988 through November 1996 received 50 mg from PD 1 through PD 10 and 40 mg beginning PD 11. Cases undergoing surgery from December 1996 through December 2001 received 50 mg from PD 1 through PD 3, 40 mg from PD 4 through PD 10, and 30 mg beginning PD 11. Cases undergoing surgery after January 2002 received 50 mg from PD 1 through PD 3, 40 mg from PD 4 through PD 7, and 30 mg thereafter. In case of acute rejection (AR), bolus administration of MPSL was given. This bolus was used in 61 patients at an average dose of 3,320 (SD 1,941, range 625–6,250) mg. The dose of MPSL depended on the severity of AR.

To examine the relationship between the development of AVN and total oral steroid dose in the first 2 weeks after renal transplantation, we divided all cases (including those that developed AVN and those that did not) into 3 groups (lower, middle, and upper tertiles) based on the dose of orally administered steroid. Incidence of AVN by 12 months postoperatively was compared among tertiles using univariate analysis and multivariate analysis adjusted for other factors. The total doses of steroid in the lower, middle, and higher tertiles in the first 2 weeks postoperatively were \leq 520 mg (average 516

mg), 520–600 mg (average 553 mg), and $>$ 600 mg (average 655 mg). Risk of AVN development in the medium-dose and higher-dose groups was compared to that in the lower-dose group.

Statistics

The relationships between AVN and age, sex, presence or absence of AR, type of transplanted kidney (living or cadaveric), type of immune suppressor used (cyclosporine or tacrolimus), and steroid dose were compared by univariate analysis (crude odds ratio (OR)) and multivariate analysis (adjusted OR), adjusting for other factors. ORs and 95% confidence intervals (CIs) were calculated using a conditional logistic regression model. These analyses were performed using SAS software version 6.12. We considered *p*-values less than 0.05 to be statistically significant.

Results

MRI performed preoperatively or at 4 weeks postoperatively did not reveal any band patterns in T1-weighted images. By 12 months postoperatively, 48 patients (mean age 39 years) had band patterns in T1-weighted images and 238 patients (mean age 38 years) had no band patterns. 45 of the 48 patients showed demarcating sclerosis in the femoral head by radiography or “cold in hot” appearance by bone scan. 3 patients had no abnormal patterns in radiographs and bone scan; however, low-intensity band on the T1-weighted image in MRI was observed at least twice. The incidence of femoral head AVN was 17%. Of the 48 patients with AVN, MRI of the hips was performed in 34 of them 6–12 weeks after renal transplantation. In those images, 29 patients had band patterns and 5 patients had not. 38 patients underwent MRI until 24 weeks; 35 patients showed band patterns. All 48 patients underwent MRI until 12 months after surgery and showed band patterns in T1-weighted images. A large proportion of the patients developed AVN at an early stage after renal transplantation. There was no relationship between steroid dose and the time taken for AVN to develop.

There were no statistically significant correlations between the development of AVN and age, sex, absence or presence of AR, type of transplanted kidney, or type of immune suppressor used (Tables 1–5).

The incidence of AVN was 6% in the lower-dose group, 17% in the middle-dose group, and 28% in the higher-dose group. AVN development in the middle-dose group was higher than that in the lower-dose group (crude OR = 3.1, *p* = 0.03; adjusted OR = 2.9, *p* = 0.04). The OR for AVN development in the upper-dose group was significantly higher than that in the lower-dose group (crude OR = 6.2, *p* < 0.01; adjusted OR = 4.9, *p* < 0.01). In addition, a statistically significant dose-response relationship was found between AVN development and the total dose of steroid administered in the first 2 weeks

Table 1. Relationship between age and development of AVN. Adjusted for sex, acute rejection, donor, immune suppressor, and steroids at 2 weeks

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age per 1 year	1.02 (0.99–1.04)	0.2	1.02 (0.99–1.05)	0.1

Table 2. Relationship between sex and development of AVN. Adjusted for age, acute rejection, donor, immune suppressor, and steroids at 2 weeks

	AVN n (%)	No AVN n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Male	30 (16)	153 (84)	1		1	
Female	18 (18)	85 (83)	1.1 (0.58–2.1)	0.8	1.1 (0.53–2.2)	0.9

Table 3. Relationship between an episode of acute rejection (AR) and development of AVN. Adjusted for age, sex, donor, immune suppressor, and steroids at 2 weeks

AR	AVN n (%)	No AVN n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
No	39 (17)	186 (83)	1		1	
Yes	9 (15)	52 (85)	1.1 (0.49–2.4)	0.8	0.55 (0.23–1.4)	0.3

Table 4. Relationship between donor type and development of AVN. Adjusted for age, sex, acute rejection, immune suppressor, and steroids at 2 weeks

Donor	AVN n (%)	No AVN n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Cadaveric	8 (28)	21 (72)	1		1	
Living	40 (16)	217 (84)	0.47 (0.19–1.1)	0.09	1.17 (0.43–3.3)	0.8

Table 5. Relationship between the type of immune suppressor and development of AVN. Adjusted for age, sex, acute rejection, donor, and steroids at 2 weeks

	AVN n (%)	No AVN n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Tacrolimus	11 (11)	86 (89)	1		1	
Cyclosporine	37 (20)	152 (80)	1.8 (0.79–3.4)	0.2	1.6 (0.75–2.6)	0.3

Table 6. Relationship between steroid dose within 2 weeks and development of AVN. Adjusted for age, sex, acute rejection, donor, and immune suppressor

Dose (mg)	AVN n (%)	No AVN n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
≤ 520	6 (6)	90 (94)	1		1	
≤ 600	16 (17)	80 (83)	3.1 (1.3–3.9)	0.03	2.9 (1.2–10)	0.04
> 600	26 (28)	68 (72)	6.2 (2.1–1.14)	< 0.01	4.9 (1.6–11)	< 0.01

after surgery ($p < 0.01$ and $p < 0.01$) (Table 6).

On the other hand, the incidence of AR was 19 in 94 patients (20%) in the lower-dose group, 22 in 96 patients (23%) in the middle-dose group, and 23 in 96 patients (24%) in the higher-dose group. There was no significant relationship between the incidence of AR and the total dose of steroid in the first 2 postoperative weeks.

Discussion

Risk factors including steroid administration, duration of hemodialysis before transplantation (Patton and Pfaff 1988), number of acute rejection episodes (Harrington et al. 1971, Tang et al. 2000), hyperparathyroidism (Chatterjee et al. 1976), and hypophosphatemia (Briggs et al. 1972) have been reported for AVN development after renal transplantation. To investigate the relationship between steroid dose and development of AVN after renal transplantation, Harrington et al. (1971) analyzed risk factors in 169 subjects. They reported that steroid dose is one of the risk factors for AVN development, since AVN occurred in 16 of 68 cases in the group that received a mean total dose of 2,960 mg in the first 3 postoperative weeks and in only 2 of 101 cases in the group that received a mean total dose of 1,180 mg. Pierides et al. (1975) examined 78 patients who had undergone renal transplantation and reported that total steroid dose in the first 3 months postoperatively was higher in the group that developed AVN than in the group that did not. Tang et al. (2000) examined 397 renal transplantation patients and found that AVN development was related to the total dose of oral steroid in the first postoperative year and to the average daily dose.

In our previous study, total steroid dose in the first 8 weeks postoperatively was found to be related to AVN development, but no statistically significant relationship was observed between steroid dose in shorter postoperative periods and AVN development (Shibatani et al. 2008). In the present study, we extended our focus of analysis to patients who underwent renal transplantation in the previous 2 decades at our hospital and found that the total steroid dose in the first 2 weeks postoperatively has a statistically significant correlation to AVN development, and that there is a dose-response relationship between them.

Mean total daily steroid doses in the lower-, middle-, and higher-dose groups were calculated to be 37 mg, 40 mg, and 47 mg. The difference in the daily dose between the lower-dose and middle-dose groups was 4 mg and that between the lower-dose and higher-dose groups was 10 mg. The incidence of AVN in the lower-, middle-, and higher-dose groups were 6%, 17%, and 28%. The incidence in the middle-dose group was about 2 times greater, and that in the higher-dose group about 4 times greater, than that in the lower-dose group, demonstrating that a small difference in dose yielded a large change in incidence. With the improvements in immune suppressors, total steroid dose after renal transplantation has become lower in recent times. In the present study, azathioprine (from 1988 to 2000), mycophenolate mophetil (from 2000 to 2002), and mycophenolate mophetil or mizoribine and basiliximab (from 2002 to 2007) were administered as immune suppressor, together with cyclosporine or tacrolimus. Thus, the incidence of AR did not increase in the lower-dose steroid group. We therefore consider it important to reduce the steroid dose as much as possible during the early postoperative period in order to reduce the risk of development of AVN.

In the setting of systemic lupus erythematosus (SLE), the corticosteroids dose ingested in the first month, the first 3 months, and the first 6 months had stronger correlation to the development of AVN than the total dose of steroid during therapy (Abeles et al. 1978). In our renal transplantation cases, the first doses of oral PSL were 50 mg in all cases, but the subsequent PSL administration schedules were different in the 3 groups. After renal transplantation, oral steroid doses were decreased day by day. Thus, we considered the total steroid dose in the first 2 weeks after operation to be the initial dose in the renal transplantation cases.

Many previous studies of AVN after renal transplantation have included only symptomatic cases with plain radiographs; thus, the incidence of AVN in groups including asymptomatic cases has not been accurately evaluated. Sugano et al. (1999) demonstrated that MRI has a high sensitivity and specificity in the diagnosis of AVN; thus, MRI is suitable for accurate diagnosis. In our study, 48 of 286 patients had band patterns in T1-weighted images. 45 of the 48 patients showed demarcating sclerosis in the femoral head in radiographs or “cold in hot” appearance by bone scan. 3 patients did not show abnormal patterns in radiographs or bone scan, but low-intensity banding on the T1-weighted image in MRI was observed twice or more. We therefore in this study we screened AVN development after renal transplantation using MRI and therefore believe that the incidence of AVN development has been accurately assessed in our study. Among the previous studies of AVN after renal transplantation using MRI, one study using multivariate analysis demonstrated a relationship between AVN development and delayed graft function (Takao et al. 2011). We found a correlation between AVN development and steroid dose in the early postoperative period, and we also showed a dose-response relationship.

Band patterns on MRI correspond to repair tissues found between necrotic and intact areas (Hauzeur et al. 1992, Kubo et al. 2000). Thus, there would be a time lag between the occurrence of ischemia and the appearance of the band pattern. It has been reported that 1 month after internal fixation of a fracture of the femoral neck, band patterns on MRI can be seen in the femoral head away from the fracture line (Sugano et al. 1996). In patients who develop AVN after renal transplantation, it is presumed that intraosseous ischemia occurs earlier than 6–12 weeks postoperatively (Kubo et al. 1997, Fujioka et al. 2001) when band patterns are observed on T1-weighted MRI. In experiments with animal models of osteonecrosis, Ichiseki et al. (2005) and Kabata et al. (2008) showed that intraosseous ischemia occurs quite soon after administration of large doses of steroid; on the fifth day and the third day, respectively, after steroid administration. We found that the total dose of steroid administered in the 2 weeks after the renal transplantation is related to AVN development. This result suggests the occurrence of an event in the bone that may lead to the development of AVN at a very early period after steroid administration. We believe preventive measures should be taken in the short period before and just after steroid administration.

KU, MI, and KI collected data. TG and WF analyzed the data. YA and HF collected some data, wrote the manuscript, and reviewed subsequent drafts. MF and TK participated in acquisition of data and reviewed the manuscript.

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