Intravenous Methylprednisolone for Kidney Transplantation

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The effect of different dosage levels (0-100 mg/kg/day x 3) of intravenous methylprednisolone was tested in canine kidney autografts undergoing immediate contralateral nephrectomy. Intravenous methylprednisolone was safely administered in doses up to 40 mg/kg/day for three days after kidney transplantation. Higher doses (40 mg/kg/day x 3) were functionally and structurally harmful to canine kidney autografts.

Intravenous methylprednisolone (IVMP) is used routinely in clinical transplantation for treating kidney allograft rejection.\textsuperscript{1,2,6,7} Although significant knowledge is being accumulated about the effect of IVMP on renal allograft survival,\textsuperscript{1,2,6,7} there are practically no studies on the safest intravenous pulse dose. Isolated reports in the literature\textsuperscript{a} indicate that 40 mg/kg/day on the first three postoperative days and at the time of rejection could be harmful to human kidney allografts. However, others\textsuperscript{c} have shown that 30 mg/kg of methylprednisolone as a single large intravenous injection is not harmful to normal individuals. This study systematically compares the effect of various pulse doses of IVMP (0 to 100 mg/kg/day for three days) given to canine kidney autografts in order to determine the safest pulse dose of IVMP for kidney transplantation.

\section*{Material and Methods}

Adult mongrel dogs of either sex, weighing between 14 and 23 kg, were anesthetized with sodium thymalal for induction and fluothane (0.5-1.5\%) for maintenance. These dogs were maintained by endotracheal intubation, and oxygen was given continuously during anesthesia. Five hundred to 750 ml of Ringer's lactate were administered during surgery and for the first 12 hours thereafter. Through a midline laparotomy, the left kidney was dissected using the "non-touch" technique, then removed, and flushed with 250 ml of Ringer's lactate (containing heparin 10,000 U/L) at 4°C. It was then autotransplanted into the right iliac fossa in a routine manner at the same time as the contralateral kidney was removed. Immediately before kidney removal and after transplantation 10 mg of furosemide were given intravenously. All dogs were followed daily for symptoms of renal failure. Daily serum creatinine levels were obtained for the first 10 days, then every other day until death or sacrifice at 20 days. Kidney biopsies for light microscopy were obtained at one hour, two hours, three days, and one week after transplantation. All dogs underwent postmortem examination, and kidney samples were again obtained for light microscopy.
Five groups of animals were studied. Group I was a control group of four dogs that received no methylprednisolone. Groups II to V were divided according to the amount of methylprednisolone each dog received on the day of transplantation and for two consecutive days thereafter. Group II (4 dogs) received 20 mg/kg/day; Group III (4 dogs) received 40 mg/kg/day; Group IV (6 dogs) received 70 mg/kg/day; and Group V (6 dogs) received 100 mg/kg/day. The Student’s t-test was used to compare statistically all the variables obtained.

**Results**

Control kidneys and those treated with 20 mg/kg/day of methylprednisolone showed normal serum creatinine values after transplantation (Figure 1). There were no daily differences (p > 0.8) in the serum creatinine values between these two groups of dogs. The survival was 100% in both groups. Dogs treated with 40 mg/kg/day of methylprednisolone showed no significant differences (p > 0.5) in renal function when compared to the control dogs or those treated with 20 mg/kg/day (Figure 1). All dogs in this group survived also. However, significant daily differences (p < 0.05-0.001) in serum creatinine were observed between the control dogs and those in Group IV and Group V (Figure 1).

In Group IV (70 mg/kg/day), one of six animals died on the seventh postoperative day, and in Group V (100 mg/kg/day), two of six animals died on the sixth and seventh postoperative days. All exhibited rapid and progressive renal failure after transplantation.

Almost no abnormal histological findings were seen in Groups I, II, and III (Table I). Groups IV and V, which had been treated with very high concentrations of methylprednisolone (> 40 mg/kg/day), showed exudation with 4 to 6 PMNs per glomeruli (5/12, 41%), collapse of capillary loops (7/12, 58%), and eosinophilic amorphous deposits (6/12, 50%) in the first few hours after transplantation (Table I). Interstitial edema and focal hemorrhages were also seen frequently (Figures 2,3).

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**Fig. 1**

Daily serum creatinines after kidney autotransplantation of control dogs and those treated with variable pulse doses of IVMP. Significant (p < 0.05) daily differences in serum creatinine values were noted between the control dogs and those receiving 70 and 100 mg/kg/day for three days after transplantation.
**TABLE 1**

Comparative Sequential Histological Observations on Canine Renal Autografts Treated with Variable Pulse Doses of IVMP

<table>
<thead>
<tr>
<th>Time</th>
<th>Structure</th>
<th>Control</th>
<th>20 mg/kg/day</th>
<th>40 mg/kg/day</th>
<th>70 mg/kg/day</th>
<th>100 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glomeruli</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal with occasional RBC</td>
<td>2/6 exudation with hyaline casts</td>
<td>3/6 exudation with hyaline casts</td>
</tr>
<tr>
<td>1 Hr</td>
<td>Tubules</td>
<td>Normal</td>
<td>Normal</td>
<td>Occasional RBC</td>
<td>4-6 PMNs* /glomeruli</td>
<td>4-6 PMNs/glomeruli</td>
</tr>
<tr>
<td></td>
<td>Interstitium</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>2/6 edema</td>
<td>3/6 edema</td>
</tr>
<tr>
<td>2 Hr</td>
<td>Glomeruli</td>
<td>Normal</td>
<td>Normal</td>
<td>3/6 obliteration of capillary loops</td>
<td>4/6 obliteration of capillary loops</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tubules</td>
<td>Normal</td>
<td>Occasional RBC</td>
<td>3/6 exudation with PMNs</td>
<td>3/6 vacuolation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interstitium</td>
<td>Normal</td>
<td>Normal</td>
<td>3/6 vacuolation</td>
<td>2/6 edema</td>
<td>3/6 edema</td>
</tr>
<tr>
<td>3 Days</td>
<td>Tubules</td>
<td>Normal</td>
<td>Occasional RBC</td>
<td>2/6 necrosis</td>
<td>5/6 with RBCs</td>
<td>6/6 with RBCs</td>
</tr>
<tr>
<td></td>
<td>Interstitium</td>
<td>Normal</td>
<td>Normal</td>
<td>3/6 edema</td>
<td>4/6 edema</td>
<td>3/6 edema</td>
</tr>
<tr>
<td></td>
<td>Glomeruli</td>
<td>Normal</td>
<td>Normal</td>
<td>5/6 obliteration of capillary loops</td>
<td>6/6 obliteration of capillary loops and exudate</td>
<td></td>
</tr>
<tr>
<td>1 Week</td>
<td>Tubules</td>
<td>1/4 hyaline casts</td>
<td>Some RBC,* WBC,* casts</td>
<td>Hyaline casts</td>
<td>3/6 vacuolation</td>
<td>4/6 vacuolation</td>
</tr>
<tr>
<td></td>
<td>Interstitium</td>
<td>1/4 local edema</td>
<td>1/4 local edema</td>
<td>2/6 edema and hemorrhage</td>
<td>3/6 edema and hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

* RBC = red blood cells; WBC = white blood cells; PMNs = polymorphonuclear leukocytes

**Discussion**

This study shows that 20 and 40 mg/kg/day of IVMP for three days were not harmful to canine kidney autografts and appear to be the safest doses for kidney transplantation. Very high doses of IVMP (70-100 mg/kg/day for three days) were harmful to kidney autografts, with all dogs demonstrating significantly impaired renal function after transplantation. It was also evident that the increase in serum creatinine levels correlated well with the histological damage observed in these kidneys (Table I).

Several reports in the literature indicate that harmful effects of methylprednisolone in kidney allografts are evident when 40 mg/kg/day or higher doses are used. However, we were unable to find any systematic study in the literature dealing with the safest pulse dose of IVMP on autografted kidneys. In a retrospective study, Tremann and his associates observed that patients receiving 40 mg/kg/day of methylprednisolone for three days and at the time of rejection did not do as well as those receiving lower doses. They also demonstrated functional and structural kidney damage in dog kidneys perfused with more than 1 gm/L of methylprednisolone in the perfusate. Immediately after revascularization four of seven canine kidneys were normal, while three kidneys showed exudation with PMNs in the glomeruli, collapse of loops, and some eosinophilic deposits. There was also some evidence of interstitial hemorrhage in two of six dogs. These findings appear to correlate well with our pathological observations.

It is clear from other studies that a very high dose of steroids (> 30 mg/kg/day) will result in some functional and structural lesions. However, the dose of IVMP that produced damage in our animals differs from the one previously reported. We found that 40 mg/kg were not harmful to autografted kidneys in our experiments, whereas 70 mg and 100 mg/kg/day produced some kidney damage. We did not include any kidney allografts in order to eliminate the immunological mechanism which could be involved in this type of lesion.

Our study leaves no doubt about the potentially harmful effect of methylprednisolone above 40 mg/kg/day for three
Multiple abnormalities are seen: increased proteinaceous material in urinary space, visceral epithelial cell swelling, increased mesangial cells, irregular cytoplasmic vacuolization of a few proximal convoluted tubules and proteinaceous material within the lumen of tubules (HE X390).

It is possible that high concentrations of steroids cause disruption of the lysosomal membranes instead of stabilization. Other functional factors could also be present, such as a marked decrease in the creatinine clearance ratio which has been observed after the administration of prednisolone (1 gm) over one hour; this decrease was consistent with a depressed secretion of creatinine.

In summary, in this paper we demonstrate that methylprednisolone can safely be administered in doses up to 40 mg/kg/day for three days immediately after transplantation. However, IVMP at 70 and 100 mg/kg/day for three days caused functional and structural damage to canine kidney autografts.
Fig. 3
Kidney biopsy taken three days after transplantation in a dog receiving 100 mg/kg/day of methylprednisolone. Multiple abnormalities were seen: diffuse increased endocapillary cells, swelling of visceral and parietal epithelial cells, fine diffuse cytoplasmic vacuolization in tubules and irregularity and epithelial cell size and staining suggestive of acute tubular epithelial damage (HE X390).

References


