PART VI
TRANSPLANTATION—PRESERVATION
AND COMPLICATIONS
Chairman: Dr P J Ch Vereerstraeten
Experimental and Clinical Experience with Chlorpromazine Pre-treatment of Donor Kidneys

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Introduction

In Denmark, as in many other countries, the majority of transplantations are performed with cadaver kidneys, and since the death criterion for our donors is cardiac arrest, this means that most of the kidneys have been through an agonal phase, and have had a warm ischaemic period between cardiac arrest and the start of preservation.

The types of change which take place in the kidneys in these periods, and thus the causes of the varying results after transplantation, are not fully understood. It has been shown that the agonal phase as well as the warm ischaemic period result in increased vascular resistance in the kidney (Belzer et al., 1970; Løkkegaard and Bilde, 1972). This is probably due to spasm in the preglomerular arterioles secondary to such factors as hypotension, increased pCO₂, mechanical trauma of the renal pedicle, liberation of vasoactive substances locally in the kidney and anoxic damage of a contracted vascular system during the warm ischaemic period. (Løkkegaard, in press.)

The question has been asked: could renal failure after transplantation be caused by vascular spasm rather than by ischaemic damage of the renal parenchyma? The complex genesis of vascular spasm could explain why it is often difficult to correlate the length of the warm ischaemic period to onset of function of the transplanted kidney.

Since 1970 we have worked with pre-treatment of ischaemic kidneys with chlorpromazine. These experimental and clinical studies have two purposes, (1) to demonstrate that chlorpromazine improves the result of transplantation with kidneys which have been exposed to ischaemia and, (2) to elucidate whether this improvement is due to an effect on the vascular system or on the renal parenchyma.
MATERIAL, METHODS AND RESULTS

We have investigated the effect of pre-treatment with chlorpromazine 4 mg/kg intravenously before the kidneys were exposed to ischaemia.

Our investigations were divided into three parts.

(1) The influence of chlorpromazine on the vascular resistance, $^{125}$I—Hippuran uptake, and survival of kidneys with varying warm-ischaemia time without subsequent preservation.

(2) The same conditions but after 24 to 48 hr preservation using simple hypothermia and 'Collins solution' (Collins et al, 1969).

(3) Clinical experiences.

The influence on the vascular system was judged by measuring the vascular resistance. In rabbits the left kidney was isolated, ureter cut and the renal artery clamped. 0—30—45—60—120 and 180 min later the kidneys were removed, placed in a perfusion apparatus and perfused for 20 min at 9°C with low molecular weight dextran in balanced salt solution (TIS—U—SOL) using a constant flow rate of 0.5 ml/g/min. The arterial pressure was measured and the vascular resistance (VR) calculated from the formula VR = pressure/flow. Half of the kidneys were pre-treated with chlorpromazine. Five experiments were undertaken in each group. The results are shown in Figure 1.

![Graph showing vascular resistance vs time](image)

Figure 1. Vascular resistance in rabbit kidneys with 0—180 min of warm ischaemia, with and without pre-treatment with chlorpromazine. In kidneys with more than 30 min of warm ischaemia chlorpromazine significantly lowers the vascular resistance ($p < 0.01$).

In 10 cases the vascular resistance was measured in kidneys with one hour of warm ischaemia. Then the kidneys were preserved with simple hypothermia using 'Collins perfusate', and the vascular resistance measured 24 and 48 hr later
Figure 2. Vascular resistance in kidneys with one hour of warm ischaemia followed by 0–48 hr of cold ischaemia. After 24 hr of cold ischaemia the difference between the pre-treated and non-pre-treated groups was still significant (p < 0.01).

(see Figure 2). Half of the kidneys were pre-treated with chlorpromazine.

The viability of the renal parenchyma was judged by measuring the $^{125}$I – Hippuran uptake in kidney slices. Cortex slices were incubated at 25°C in a solution containing $^{125}$I – Hippuran. The activity was measured after one hour, and the uptake calculated as slice/medium ratio (Counts/g/slices ÷ counts/1 ml medium). In 70 experiments the uptake was measured 0–300 min after clamping of the renal artery. In half of the cases the kidneys were pre-treated with chlorpromazine. Figure 3 shows the results.

In similar studies (Figure 4) the kidneys were preserved for 24 hr using simple hypothermia with ‘Collins solution’ before measuring the $^{125}$I – Hippuran uptake.

In 20 rabbits the left kidney was isolated and the renal artery clamped for 180 min. Then the right kidney was removed and serum-creatine was measured every second day for 14 days. The results are shown in Figure 5. Half of the kidneys were pre-treated with chlorpromazine.

In 10 pigs the renal artery on the left side was clamped for one hour. Then the kidneys were removed, preserved for 24 hr by simple hypothermia with ‘Collins solution’ and then autotransplanted. Immediate contralateral nephrectomy was performed and the function of the preserved kidneys was followed by means of plasma creatinine (Figure 6). Half of the kidneys were pre-treated with chlorpromazine.
Figure 3. The $^{125}$I–Hippuran uptake in kidney slices with a warm ischaemic time from 0–300 min. No significant difference between the pre-treated and non-pre-treated group could be demonstrated ($p > 0.05$).

Figure 4. The $^{125}$I–Hippuran uptake in kidney slices with a warm ischaemic time from 0–240 min, followed by 24 hours of cold ischaemia. Only after 30 min of warm ischaemia was the uptake ratio slightly lower in the non-pre-treated group ($0.02 < p < 0.05$).

Finally the method was evaluated by clinical experiments. The material included 57 kidneys from donors from the neurosurgical department. Following demonstration of brain death, artificial respiration was stopped, and after cardiac arrest the kidneys were removed and preserved with simple hypothermia using
Figure 5. Serum-creatinine in rabbits following clamping of the renal artery for 3 hr and contralateral nephrectomy. All animals in the non-pre-treated group except one died of uraemia, while 6 of 10 survived in the pre-treated group.

Figure 6. Plasma-creatinine in pigs autotransplanted with kidneys exposed to one hour of warm and 24 hr of cold ischaemia. After pre-treatment with chlorpromazine all five animals survived. In the non-pre-treated group only 1 of 5 survived.

'Collins solution'. In all cases heparin and mannitol were given just before the respirator was stopped. Chlorpromazine was administered at the same time in 31 cases. After transplantation the kidney function was judged by 'day of onset'
Table I. Clinical Results With and Without Pre-treatment.

The two groups showed no difference with respect to the length of the agonal phase and the warm and cold ischaemic periods. The number of kidneys with immediate function significantly increased in the pre-treated group (p < 0.05). Because of acute rejection the five kidneys beneath the heading 'Never' are not included in the statistical calculation.

<table>
<thead>
<tr>
<th></th>
<th>Onset of function (No. of kidneys)</th>
<th>Lowest serum creatinine (mg%)</th>
<th>(SD)</th>
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<tbody>
<tr>
<td></td>
<td>Immediate</td>
<td>Delayed</td>
<td>Never</td>
</tr>
<tr>
<td>− chlorpromazine</td>
<td>14</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>(n = 26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ chlorpromazine</td>
<td>23</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>(n = 31)</td>
<td></td>
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<tr>
<td></td>
<td>37</td>
<td>15</td>
<td>5</td>
</tr>
</tbody>
</table>

(the first day the kidney was able to lower serum-creatinine) and the lowest serum-creatinine obtained. The results are shown in Table I.

**DISCUSSION AND CONCLUSIONS**

Our results show that pre-treatment of ischaemic kidneys with chlorpromazine, experimentally as well as clinically, increases the possibilities for early onset of kidney function after transplantation.

Furthermore we have demonstrated that the viability of the renal parenchyma, as judged by $^{125}$I — Hippuran uptake, is not improved after chlorpromazine pre-treatment, whereas the vascular resistance is significantly lowered in the pre-treated kidneys. This reduction in vascular resistance was maintained even after 24 hr of cold ischaemia.

These findings indicate that the improved function of ischaemic kidneys pre-treated with chlorpromazine is due to prevention of vascular spasm rather than to a direct effect on the renal parenchyma.

**Acknowledgements**

This work was supported by the Danish State Research Foundation.

**References**


Løkkegaard, H. (To be published)


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Open Discussion

CHAIRMAN Could I ask you if it would be useful to add chlorpromazine to the preservation fluid.
DAHLAGER We have tried it and it is not effective if vascular constriction has already occurred.
F P BRUNNER (Switzerland) Did you inject a vasodilator when taking out the kidneys?
DAHLAGER No.
BRUNNER Do you think chlorpromazine pre-treatment is better than, for instance, injecting an alpha-blocking agent into the renal artery before clamping?
DAHLAGER I think it is important to give vasodilators before even touching the kidney, certainly before operating on it. We use chlorpromazine in preference to phenoxybenzamine because we find it easier to control the falling blood pressure which occurs with a vasodilator.