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Reevaluation of a New Colloid Hyperosmolar Solution for Hypothermic Storage of Ischemic Canine Kidneys

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This paper describes the results of experiments designed to test the effectiveness of a new colloid hyperosmolar solution (Toledo-Pereyra) for renal hypothermic storage. Three experimental conditions were employed: 60 minutes of warm ischemia (37°C), 24 hours of hypothermic storage, and a combination of warm ischemia and hypothermic storage. Canine kidneys tolerated either one of the first two procedures when flushed with the colloid hyperosmolar solution before storage or transplantation. If warm ischemia was applied before 24 hours of hypothermic storage, four of six dogs survived more than 20 days after transplantation, while the other two died of uremia. Thus, this new solution offers a good medium for 24-hour hypothermic storage, as well as some protection from the adverse effects of warm ischemia.

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It has recently been demonstrated by Toledo-Pereyra and his colleagues1-4 that a colloid hyperosmolar solution is an adequate means for hypothermic storage not only of canine kidneys,4 but also of pancreas,1 heart,3 and lung allografts.2 They found that canine kidneys which were flushed and stored in a colloid hyperosmolar solution functioned better than kidneys stored in a crystalloid hyperosmolar solution. This paper describes the results of a randomized study to determine the effect of this new solution on canine kidneys subjected to ischemia (60 minutes), to hypothermic storage (24 hours), or to a combination of both methods before transplantation.

Material and Methods

Adult mongrel dogs of either sex, weighing between 14 and 25 kg, were anesthetized with sodium methohexital for induction and fluothane (1-0.5%) for maintenance. During anesthesia they were kept on a respirator with continuous oxygen flowing through the nasotracheal tube. During the operation, donor and recipient animals received 500-750 ml of Ringer’s lactate containing mannitol (625 mg/L) and furosemide (20 mg/L). Through a flank or midline incision, the left kidney was completely dissected. 2500 U of heparin were given intravenously. Some kidneys received warm ischemia by crossclamping both renal vein and artery and leaving the kidney in situ (37°C) until the end of ischemia. Thereafter, the kidney was excised and flushed at 4°C with 300-500 ml of the colloid hyperosmolar solution (Toledo-Pereyra). This solution basically consisted of silica gel fraction of plasma (700 ml) made hyperosmolar (420-450 mOsm/L) with albumin (25 gm/L), 5% dextrose (100 ml), and potassium chloride (40-65 mEq/L). The kidney was left in the solution at 7°C for 24 hours. At the end of this period a kidney autotransplantation was performed on the right iliac area with immediate contralateral (right) nephrectomy. Twenty mg of furosemide were given intravenously immediately before the vascular clamps were opened. After surgery, the dog’s renal function was followed by means of daily serum creatinines until its death or sacrifice at 20 days.
All animals underwent postmortem examination of the kidney with biopsy for histological studies. Biopsies for light histology and electron microscopy were also taken immediately after transplantation.

Three groups of dogs, six in each group, were analyzed. In Group I, kidneys underwent 60 minutes of warm ischemia at 37°C and were flushed with the colloid hyperosmolar solution without any hypothermic storage. In Group II, kidneys were flushed with the same solution and stored under hypothermia for 24 hours without warm ischemia. In Group III, kidneys were subjected to the same ischemic procedure as Group I, but were also stored hypothermically for 24 hours as was done for Group II. All values were statistically compared by nonparametric methods of analysis.

Two dogs died at eight days, and another dog had serum creatinine values that never returned to normal levels. Three of six dogs showed normal serum creatinine, and four of six survived 20 days after transplantation.

The histological and ultrastructural changes observed in the ischemic and preserved kidneys were variable. Glomerular damage was rarely seen, but the cells were somewhat ballooned, and the tubules were minimally damaged with the mitochondria rather washed out (Figure 2). In the kidney of one dog that died eight days after transplantation, the mitochondria were within normal limits, the endoplasmic reticulum was dilated, vesicular structures were increased, and the tubular cells were minimally distorted (Figure 3).

Results

All kidneys subjected to 60 minutes of warm ischemia before transplantation had an immediate elevation of serum creatinine in the first postoperative day, which decreased to normal values in the next two to three days (Figure 1). All dogs survived for 20 days. Kidneys stored for 24 hours hypothermically with the colloid hyperosmolar solution had a moderate elevation of serum creatinine after transplantation, which in the following days decreased to practically normal values (Figure 1). All kidneys survived for 20 days after grafting. If 60 minutes of warm ischemia and 24 hours of hypothermic storage were combined before transplantation, a significant elevation of serum creatinine was noted in the first postoperative day with a slow recovery in half of the dogs in the following four to five days (Figure 1).

Discussion

This study indicates that 60 minutes of warm ischemia alone or 24 hours of hypothermic storage alone do not cause any significant damage in function and survival of kidneys stored in a hyperosmolar colloid solution. However, when 60 minutes of warm ischemia was applied before 24 hours of hypothermic storage, a definite deterioration in kidney function was observed. This work supports the similar results we obtained in an earlier study, although the serum creatinine response after transplantation in these three different experimental groups was even better than the response reported in the previous study. Furthermore, the group in which 60 minutes of warm ischemia were combined with 24 hours of hypothermic storage had higher survival rates than those shown in the earlier report.

![Fig. 1](image_url)

Serum creatinine values of kidneys subjected to warm ischemia (60 minutes) and/or hypothermic storage (24 hours). Canine kidneys satisfactorily tolerated sixty minutes of warm ischemia alone or 24 hours of hypothermic storage. The combination of warm ischemia and hypothermic storage caused moderate damage, and only four of six dogs survived for 20 days.
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Ultrastructural morphology of a canine kidney subjected to 60 minutes of warm ischemia and 24 hours of hypothermic storage. The mitochondria appear to be somewhat washed out, but cells are ballooned, and the epithelial foot processes appear to be normal (X13200).

In Halasz and Collins’ report, all dogs survived if 20 minutes of warm ischemia were followed by 24 hours of flushing and ice storage preservation with Sacks solution, and their renal function returned to normal several days after transplantation. But if warm ischemia was combined with 48 hours of flushing and ice storage, all the transplanted dogs died of uremia. In this study, when we combined a longer period of warm ischemia (60 minutes) with a shorter period of hypothermic preservation (24 hours), our data indicated some protective effect on the kidneys in Group III after ischemic injury. Four of six dogs survived 20 days after transplantation when 60 minutes of warm ischemia were applied prior to hypothermic storage.

Sacks and his group reported somewhat different results from those of Halasz and Collins. Minimal kidney damage was observed after transplantation with 48 hours of hypothermic renal preservation preceded by 30 minutes of normothermic ischemia, and complete recovery was reported in four of five dogs. Using the Collins solution (C4), Johnson and his group reported that only two of ten dogs survived when 30 to 40 minutes of warm ischemia were followed by 24 hours of hypothermic storage and delayed nephrectomy in 19 days. Toledo-Pereyra et al. reported on the effect of 20 minutes of warm ischemia and hypothermic storage with Collins solution for 24 hours, with results similar to those of Halasz and Collins.

Our present data indicate that hypothermic storage with a colloid hyperosmolar solution can somehow protect kidney function, although it is not clear why a colloid hyperosmolar solution is similar to or even better than a crystalloid hyperosmolar solution. The hyperosmolarity of this new solution is obtained mainly by the addition of albumin, glucose, and increased cation concentration. The crystalloid solutions have increased osmolarity by adding either intracellular cations and/or mannitol.

Toledo-Pereyra et al have previously demonstrated that
hypertonic mannitol does not offer significant protective effect for ischemic kidneys. On the contrary, it can be detrimental to kidney function when the kidneys have been subjected to 20 to 40 minutes of warm ischemia before flushing and to 24 hours of hypothermic pulsatile perfusion. Sterling and his associates also demonstrated that a 7% mannitol solution was unsuccessful for renal preservation, and in certain cases caused irreversible vascular injury. It is possible that the albumin content of our solution and the high glucose and potassium concentrations offer a "desirable" protective state. The albumin might prevent leakage of fluid with high molecular weight substances into the interstitial space. The potassium might counteract the ion forces and maintain stability in the membrane, while the glucose could increase the osmolarity and offer some energy fuel if necessary.

In short, with this colloid hyperosmolar solution we obtained results similar to those observed by Toledo-Pereyra and Condie for preserved kidneys. This colloid hyperosmolar solution offers new possibilities for research using other means of hypothermic storage for organs.

References