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Effect of Glucagon and Methylprednisolone on Pancreatectomized Recipients of Whole Pancreas Allografts

Luis H. Toledo-Pereyra, MD, PhD,* Michael Zammit, MD,* and Krishna D. Valjee, MD*

Glucagon alone or in combination with methylprednisolone was an adequate therapeutic adjuvant for pancreatectomized recipients of whole pancreas allografts. All recipients were minimally immunosuppressed with azathioprine, 5.0 mg/K/day for three days, then 2.5 mg/K/day. The morphological, functional, and survival response after whole pancreas transplantation indicated a trend of improvement in the treated groups. Only the groups of dogs receiving glucagon alone or in combination with methylprednisolone survived more than two weeks after transplantation. This therapy has proven to be effective for whole pancreas transplantation.

Introduction

Many attempts have been made to protect the pancreas from severe pancreatitis, edema, and hemorrhagic necrosis after transplantation. Tersigni and his group used methylprednisolone, glucagon, and allopurinol to protect pancreaticoduodenal allografts preserved by hypothermic pulsatile perfusion for twenty-four hours. Recently, Kyriakides and his colleagues analyzed the beneficial effect of glucagon, trasylol, and steroids in duct-ligated, porcine pancreas transplants. We used mongrel dogs whose pancreatic ducts were not ligated. This work was designed to evaluate the effect of glucagon alone or in combination with methylprednisolone on the survival of pancreatectomized recipients of whole pancreas allografts.

Material and Methods

Adult mongrel dogs of either sex, weighing between 15-25 kg, were anesthetized with sodium thiamylal for induction and halothane (0.5-2.0%) for maintenance. Donor dogs received 500-750 ml of Ringer's lactate during the operation. Total pancreatectomy was performed according to Aquino's technique. No warm ischemia was applied. A cuff of celiac trunk and portal vein was obtained for the vascular anastomosis. After the organ was removed, it was flushed with cold (4°C) Ringer's lactate (200 ml) containing heparin (10,000 U/L), procaine (0.1 g/L), and methylprednisolone (250 mg/L) buffered with bicarbonate to a pH of 7.4.

After total pancreatectomy, the pancreas from the donor animal was placed into the right iliac fossa with vascular continuity established between the host's right common iliac artery end-to-end to the celiac trunk and the donor's portal vein end-to-side to the inferior vena cava. The pancreatic duct was implanted using a technique modified from the one described by Aquino. Almost all of the papilla was eliminated in order to leave the duct alone for the anastomosis with the jejunum or ileum. No blood transfusions were given. The recipient dogs received approximately 750 ml of Ringer's lactate with dextrose 5% during
Toledo-Pereyra, Zammit, and Valjee

CAUSES OF DEATH OF ALL CANINE PANCREAS TRANSPLANTS*

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* This count excludes five dogs that died of unrelated or technical failures in the first three days posttransplantation.

The causes of death of all dogs included in this study are listed in the accompanying table. Five dogs that died of unrelated or technical failures in the first three days after transplantation were eliminated from this study. The causes of death were venous anastomotic bleeding (one dog from Group II), pancreatic duct leakage and peritonitis (two dogs from Group I, one dog from Group III), and anesthetic death (one dog from Group II).

Three groups of eight dogs each were studied. Group I, the pancreas transplant control, received no treatment except for minimal immunosuppression. In Group II, donor dogs received glucagon (1 mg) infused intravenously in saline for over one hour, thirty minutes before and during pancreas excision, with a total infusion rate of 40 μg/kg/h. Thereafter, the recipient animal received the same intravenous infusion during transplantation and 2 mg IM every six hours daily for three days. In Group III, donor and recipient dogs were pretreated with 30 mg/K of methylprednisolone two hours before pancreatectomy in addition to receiving glucagon in the same dosages as the dogs in Group II. Thereafter, 500 mg IV were given during transplantation and 250 mg IM twice a day for three days afterwards.

Results

Figure 1 shows the survival rates for all groups of dogs. The animals transplanted with pancreases treated with glucagon survived longer (p>0.08) than those in the untreated group. The addition of methylprednisolone to glucagon improved survival results even more when compared to the control group (p>0.01) or to the group treated with glucagon alone (p>0.1).

The blood glucose levels (Figure 2) were within normal limits in all groups of dogs for the first five days post-transplantation. Thereafter, at one week after surgery, higher levels were observed in the control than in the treated groups (p>0.1->0.8). A continuous rise was observed from one week post-transplantation until death (Figure 2).

The serum amylase levels (Figure 3) were normal in all groups only for the first two days post-transplantation. Thereafter, there was a steady and continuous increase, which was more dramatic at day 10 (Figure 3). Higher levels were observed in the control group than in the treated group of animals at days 7, 10, and 15 post-transplantation (p>0.08->0.1). No difference (p>0.5) was noted between the two groups of treated dogs at any time after transplantation.

There were no significant differences (p>0.1->0.8) noted in the white blood cells between the three groups of animals. However, at one week post-transplantation higher levels were observed in the control group (24,050±1275 x mm) (M±SE) than in the treated groups (18,785±1067 x mm) (M±SE) (p>0.1). No significant changes (p>0.1->0.8)
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Fig. 2
Average blood glucose levels in all groups of animals. A delayed increase in blood glucose was observed in the treated groups.

were observed in the hematocrit of all dogs after transplantation.

Histologically, the pancreas of the control transplant dogs showed some duct dilatation, edema, lymphocytic infiltration, and architectural distortion (Figure 4). The groups treated with glucagon alone showed minimal duct dilatation and edema; cellular infiltration was not prominent, and architectural changes were moderate. The group treated with glucagon and methylprednisolone had no edema, and duct dilatation was occasionally seen. Cellular infiltration in this group was less significant than in Groups I and II. There were minimal to moderate architectural changes (Figure 5).

Discussion
This study confirms that glucagon alone or in combination with methylprednisolone is beneficial for canine pancreas transplantation. Morphological and functional response after transplantation, as well as the survival results, indicated improvement in the canine grafts treated with glucagon alone or combined with methylprednisolone.

The mechanism of action of glucagon in improving pancreas transplant survival is not known. Glucagon has a definite effect in reducing exocrine pancreatic function. It affects the rate of flow, bicarbonate concentration, and rate of enzyme secretion by the pancreas with and without inflammation. It has been postulated that glucagon activates cyclic 3',5'-AMP by increasing the activity of adenyl cyclase. This might also be an important factor.

The most effective dosage of glucagon has not been worked out, and it is necessary to develop a good method to maximize its effect on pancreatic transplantation. Thirty minutes after the infusion has been administered glucagon practically disappears from the circulation. Its short-lasting effect has to be considered for studies like this which are designed to protect pancreatic allografts for transplantation. Thirty to forty mg/K/hour appear to cause a significant inhibitory effect on pancreatic secretion. However, Kyriakides and his associates demonstrated that 2 mg of glucagon administered IM daily were effective for autografts, but had no beneficial effect on allografts. Increasing the dose to 4 mg twice a day was also ineffective in preventing pancreatic fluid accumulation, although it appeared to prevent hyperamylasemia. When the same total dose was administered more frequently (2 mg IM every six hours), significant decrease in fluid accumulation around the pancreas was observed. From the work of Kyriakides et al and from other studies, it appears that a dosage of 2 mg IM every six hours is the most adequate way to treat pancreatic allografts at the present time.

The beneficial effect of steroids on pancreas allografts is probably due to the anti-inflammatory and membrane stabilizing properties of these substances. In addition, it is possible that their immunosuppressive effect could be an important factor in the prolongation of survival. Although there is some evidence in the literature that steroids can cause pancreatitis, in our work and others their beneficial effect has been well established. The question is not whether steroids are beneficial, but mainly what is their most effective use in terms of dosage and timing.

In summary, canine pancreas allografts survived an average of 11.6 days when no treatment was given except minimal
Fig. 4
Histological appearance of an untreated pancreas several days posttransplantation (X325). Note architectural distortion and poor preservation of acini and islets.

Fig. 5
Histological appearance of pancreas treated with glucagon and methylprednisolone several days posttransplantation (X325). Good preservation of islets and acini is observed.
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immunosuppression. The administration of glucagon prolonged survival to an average of 16.8 days. The combination of glucagon and methylprednisolone was even more effective, improving pancreas allograft survival to an average of 19.5 days. Thus, it is evident that glucagon alone or in combination with methylprednisolone is an adequate therapeutic adjuvant for canine pancreas allografts.

References


