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# Euro-Collins Solution for a Lower-Cost Preservation of Donor's Pancreas

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## Abstract

This paper aims to evaluate results from pancreas-kidney transplants, in type 1 diabetes mellitus patients, comparing the use of Euro-Collins and Belzer or Celsior solutions for organ storage while awaiting transplant. One hundred and twenty two transplants were performed by the same transplant group, between November 2006 and June 2011. All pancreas grafts were perfused during the harvesting process through infusion of the aorta using standard solutions (Belzer or Celsior). Fifty-seven pancreas graft were stored in Euro-Collins solution (EC Group) and sixty six stored with Belzer or Celsior solutions (BC Group). The parameters analyzed were: postoperative complications, graft loss, mortality, hospitalization time and three-month follow-up period. The average cold ischemia time was 15.25 ± 1.98 hours in EC Group and 15.3 ± 2.66 hours in BC Group. The mortality rate was 15.8% in BC Group and 9.2% in EC Group. The loss of graft was 16.9% in EC Group and 8.8% in BC Group. The average hospitalization time was 13.8 days in EC Group and 18.4 days in BC Group. No significant statistical difference was observed in any parameters. It could be concluded that the use of Euro-Collins solution to store pancreas could be used without compromising the outcome of transplants.

**Keywords:** Transplantation; Pancreas transplantation; Organ preservation solution; Kidney transplantation

## Introduction

Type 1 diabetes mellitus (DM1) is prevalent in most ethnic groups, with the highest rates observed in Nordic countries and ranging from 21.2 to 36.8 new cases per 100,000 inhabitants worldwide. Brazil has an incidence of DM1 of eight new cases per 100,000 inhabitants [1]. The disease is the most important cause of chronic kidney failure, besides being associated to various morbidities, mainly those related to neuro-vascular problems [2].

Despite the intense efforts made by patients to rigorously control blood glucose levels, patients suffering episodes of severe hypoglycemia are common, indicating that exogenous insulin replacement is not a perfect solution [3].

Pancreas transplants are considered an established therapeutic modality effective in the treatment of DM1. A successful transplant can establish a state of normoglycemia improving patient's quality of life [4].

According to the American Association of Diabetes, the combined pancreas and kidney transplant is the treatment of choice for DM1 in patients with terminal kidney disease [5].

Two steps are crucial for the success of a combined transplant during the process of acquiring and storing the donating pancreas, the perfusion and storage. Solutions that have been specially developed to maintain the biochemical and physiological conditions of the graft are used during the process. The Collins solution, developed in the 1970s, was widely used in the clinical practice of transplants until the emergence of the Belzer solution [6].

The Collins solution is simple, crystalloid, has high potassium and low sodium concentrations to mimic the intracellular environment, and high glucose concentration. This solution has undergone several modifications, including the removal of magnesium from its original formulation when it was then named Euro-Collins solution [6].

The Belzer solution, also known as the University of Wisconsin solution (UW solution), was the first solution carefully developed to preserve pancreatic grafts for transplantation. It is considered the gold standard solution for the preservation of grafts. The Celsior solution is a low viscosity preservation solution originally developed to preserve donated hearts for transplant. However, this solution has also been used successfully to preserve other organs such as liver, pancreas, and kidney [7]. Even though the use of the Belzer/Celsior solutions allows the donating pancreas to be used after longer preservation times [8], they cost significantly more when compared to the Euro-Collins solution that has been widely used in the past.

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The preservation solution, used during storage of the organ after being harvested, is used with the purpose of bathing the collected organ at 4° C, while the organ is waiting for revascularization.

Storage solution becomes an important factor when using machines for organ perfusion during storage. However, such machines are not used when storing the pancreas. Therefore, in this case, storage solution is used simply to keep the organ soaked in an isotonic solution at 4° C.

Some studies have tried to minimize the cost of the procedure by using the Euro-Collins solution in the first washing for replacement of blood in the perfusion process during collection [9,10] however, little has been studied about the solutions used in the process of storage.

Although transplant of the pancreas is gaining popularity, partly due to the number of centers around the world performing this procedure, it still has the highest rate of surgical complications among all solid organ transplants and represents a high-cost procedure [11]. In the United States, the current average cost of pancreas-kidney transplant during hospitalization time is between $110,000.00 and 125,000.00 [12].

In Brazil, the Belzer solution is 7 times, and the Celsior solution is 18 times the cost of the Euro-Collins solution. Therefore, the use of the Euro-Collins solution represents a significant reduction in cost. Few studies have compared the use of these three solutions for organ storage. In this study, we aimed to evaluate the use of Euro-Collins solution for storing the pancreas following the use of the Belzer or Celsior solutions in aortic perfusion during the harvesting process, and compare the outcomes when the Belzer or Celsior solutions are used during storage.

## Materials And Methods

This retrospective and sequential study examined the medical records of 122 patients who received pancreas-kidney consecutive transplants, from November 2006 to June 2011, in the Kidney Hospital from the Federal University of São Paulo, Brazil.

The patients were divided in two groups according to the liquid utilized in the storage of the pancreas. In a sequential manner, the first sixty five grafts were stored in Belzer or Celsior solutions (BC Group) and the following fifty-seven organs were stored in Euro-Collins solution (EC Group).

Subjects with type I diabetes mellitus, younger than 50 years and presenting terminal kidney insufficiency were included in the study. Subjects presenting non correctable coronary artery disease (determined by angiography), an ejection fraction lower than 50%, recent myocardial infarction, psychiatric disease, previous history of difficulty to adhere to the treatment, current cancer or infectious disease, morbid obesity (body mass index less than 40), or using drugs (alcohol included) were not included in the study.

All grafts were perfused during the harvesting process through infusion of the aorta using standard solutions (Belzer or Celsior) as described previously [13].

After performing a median infra umbilical and supra umbilical abdominal incision, the pancreatic implantation process was done through vascular anastomoses between the graft portal vein and the recipient cava or right common iliac veins, and between the graft artery and the recipient iliac artery. Enteric drainage of the exocrine pancreatic secretion was performed. Antibiotic prophylaxis was administered for 72 hr. Tacrolimus (FK 506), steroids, and microphenolate were used for immunosuppression.

All patients analyzed in this study followed previously established protocols for donor's parameters, surgical technique, and post-operative procedures. The patients were all transplanted by the Transplant Group that teaches the Surgical Gastroenterology course at the Federal University of São Paulo, at the Kidney and Hypertension Hospital, Oswaldo Ramos Foundation, Brazil.

The data in the patient's medical records included all daily laboratory tests such as blood, glucose, amylase, lipase, sodium, potassium, and serum creatinine tests. Ultrasound, Doppler, and CT scans of the abdomen were performed only when clinically indicated.

Data from clinical, demographic, and surgical parameters were collected during a three-month period of the patients' follow-up.

### Analyzed complications

**Pancreatitis**: All patients who presented serum amylase level at two and a half times above the normal serum value starting on the second day after surgery, even if clinically asymptomatic.

**Leaks of pancreatic or enteric origin:** The abdominal drain was removed around the third postoperative day. If a high level of amylase was found in the draining liquid, preventing its removal, then the fistula was considered of pancreatic origin. Fistulas found in the transplanted duodenum or enteric anastomosis were considered of enteric origin.

**Abdominal collection**: All abdominal collection that required surgical or percutaneous drainage.

**Reoperation:** All patients who underwent reoperation, regardless of the reason, however, because some alteration was detected; laparotomies without intra-abdominal alterations were discarded.

**Loss of pancreatic graft**: All patients having undergone pancreatectomy, regardless of its cause.

**Vascular thrombosis**: All patients having undergone pancreatectomy, whose medical records for the anatomopathological exam could confirm this diagnosis.

**Deaths**: All patients who died in the first month of follow-up, regardless of the cause of death.

### Statistical analysis

The categorical variables were presented as frequency and percentage, and the comparisons between groups were analyzed

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with the Pearson Chi-square test or *Fischer's* Exact test depending on the number of observations. The parametric continuous variables were presented as averages and standard deviation, and the comparisons between groups through the unpaired *Student*'s t-test. The non-parametric continuous variables were expressed as median and 1° and 3° quartiles, and the comparisons between groups through the Mann-Whitney test.

We adopted a $p < 0.05$ value as significant. The statistical analyses were performed with the SPSS v.18.0 software for Windows.

### Ethics

This research project was approved by the Research Ethics Committee of the Federal University of São Paulo (Protocol # 0922/10).

## Results

The average age among patients was 37.5 ± 8.8 years in the standard group (BC) and 36.6 ± 7.1 in the Euro-Collins group (EC). The gender distribution was 29 females (44.6%) and 36 (55.4%) males in BC Group and 18 females (31.6%) and 39 males (68.4%) in EC Group. There was no difference between the studied groups with respect to age and gender (Table 1).

The average diagnosis time of DM1 was 22.6 ± 7.1 years for patients in the BC Group and 23.4 ± 4.8 years in the EC Group. The average donor age was 29.9 ± 8.7 years in the BC Group and 29.0 ± 9.5 years in the EC Group. The groups did not differ in relation to time with DM1 and donor's age (Table 1).

**Table 1:** Data of the comparision between the two groups studied.

| | Belzer / Celsior | Euro Collins | p value |
|---|---|---|---|
| Number | 65 | 57 | |
| Sex, n (%) | | | |
| *Male* | 36 (55,4) | 39 (68,4) | 0,140 |
| *Female* | 29 (44,6) | 18 (31,6) | |
| Age of receptor (years) | 37,5 ± 8,8 | 36,6 ± 7,1 | 0,553 |
| Time of Diabetes Mellitus (years) | 22,6 ± 7,1 | 23,4 ± 4,8 | 0,460 |
| Time of dialysis (month) | 36,7 ± 17,2 | 42,8 ± 20,7 | 0,077 |
| Age of donor (years) | 29,9 ± 8,7 | 29,0 ± 9,5 | 0,215 |
| Time of hospitalization | 18,4dias. | 13,8 dias | 0,098 |
| Time of cold ischemia (hours) | 15,1 ± 2,9 | 14,8 ± 1,9 | 0,460 |
| Vein drainage, n (%) *Cava* | 14 (21,5) | 6 (10,5) | 0,216 |
| *Iliaca right vein* | 46 (70,8) | 44 (77,2) | |
| Pancreatitis | 0 (0) | 1 (1,8) | 0,284 |
| Reoperation | 11 (16,9) | 7 (12,3) | 0,471 |
| Vascular thrombosis | 3 (4,6) | 1 (1,8) | 0,376 |
| Leak pancreática | 4 (6,2) | 4 (7,0) | 0,848 |
| Leak entérica | 1 (1,5) | 2 (3,5) | 0,483 |
| Collections | 1 (1,5) | 3 (5,3) | 0,249 |
| Graft lost | 11 (16,9) | 5 (8,8) | 0,183 |
| Mortality | 6 (9,2) | 9 (15,8) | 0,696 |

The average hospitalization time was 13.8 days with a median of 9 days in the EC Group, and 18.4 days with a median of 13 in the BC Group. The *Student*'s t-test revealed no statistically significant difference ($p = 0.098$) between groups (Table 1).

The average cold ischemia time during graft submission was 15.1 ± 2.9 hours in the BC Group and 14.8 ± 1.9 hours in the EC Group. Venous drainage using the inferior vena cava was performed in 14 patients (21.5%) in the BC Group and 6 in the EC Group (10.5%). The groups did not differ with respect of type of transplant, cold ischemia time, and venous drainage used.

None of the patients in the BC Group and only one in the EC Group presented acute pancreatitis. No statistically significant difference was found between groups ($p = 0.284$).

Four patients were identified in each of the Groups (EC and BC, 6.2% and 7.0%, respectively) with pancreatic fistula due to the drain kept for more than 3 days during the post-operative period. No statistically significant difference was observed in the number of fistulas between the studied groups ($p = 0.848$).

Three patients from the EC Group (5%) and one from the BC Group (1.5%) presented abdominal collection. No statistically significant difference was observed in abdominal collections between the studied groups ($p = 0.249$).

Seven patients underwent reoperation, regardless of the cause, in the EC Group (12.3%) and 11 in the BC Group (16.9%). No statistically significant difference was observed between the studied groups ($p = 0.471$).

Sixteen pancreatic grafts were lost: 11 in the BC Group (16.9%) and 5 in the EC Group (8.8%). In the BC Group, 5 pancreases were secondarily lost through death, 4 by vascular thrombosis, and none due to enteric fistula. No pancreas was lost because of venous thrombosis in the EC Group. The statistical analysis showed no difference between the studied groups ($p = 0.183$). The two groups received the same immunosuppression scheme and surgical technique.

The mortality rate was 9.2% in the EC Group and 15.8% in the BC Group during the 3-month follow-up period. Although the BC Group showed greater mortality rate than the EC Group, there was not sufficient statistical power to validate this difference ($p=0.69$).

## Discussion

Three basic principles should be taken into consideration in the process of organ preservation: hypothermia, prevention of cellular edema, and biochemical effects. Hypothermia slows the effects of ischemia, however it slows down the metabolism and inhibits the sodium and potassium pump in the membrane, which is related to one of the reasons responsible for the occurrence of cellular edema. The breakdown of glucose, by anaerobic process, is stimulated during ischemia. At this point, the use of preserving solutions becomes important [14].

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Preserving solutions, containing osmotically active substances to prevent water entry into ischemic cells, have been extensively studied. According to Belzer [12], the goal of preserving an organ to be transplanted is to increase organ availability with maximum quality and at the lowest cost.

The effectiveness of the Belzer solution for the preservation of organs revolutionized the practice of transplants; it became the gold standard for the preservation (perfusion and storage) of abdominal organs [8], however, its high cost is an inconvenience even for developed countries [15]. Despite Belzer solution being the recommended solution, the Euro-Collins solution has a lower cost and can be manufactured in Brazilian institutions.

The use of the solution known as PFC (perfluorochemical oxygen carrier solution) was adopted for pancreas preservation when the organ is used as a source of pancreatic islets to identify a more efficient way to minimize the deleterious effects of ischemia during the storing process. This solution has greater capacity to store and dissolve oxygen as demonstrated in some experimental studies and to increase the level of adenosine triphosphate (ATP) in the pancreas, if compared with the Belzer solution [16,17].

Despite the concept that a pancreas stored in PCF solution is superior to another stored in the Belzer solution because of its high oxygen diffusion capacity, a single randomized prospective study comparing these two solutions did not show statistically significant differences in the quality of isolated pancreatic islets. Each of these groups of pancreatic islets performed equivalently *in vitro* and in transplanted patients [18]. In addition, another retrospective study with 200 pancreatic islet isolations did not show a difference between the different forms of storage [19]. Therefore, in the absence of a perfusion device, the solution used to store pancreases has the main objective of preserving the organ at 4°C. It becomes unnecessary to use one litre of Belzer/Celsior solution for this purpose.

In this study, we observed that the Euro-Collins solution was as efficient as the Celsior/Belzer solutions, currently considered the gold standard to preserve the pancreas. The mortality rate is still a little high in our institution when compared with data from developed countries; however, we believe that it is due to the high average of ischemia time. Thus, approximately 40% of these recipients needed dialytic therapy postoperatively, which contributes to longer hospitalization time, and increased morbidity and mortality. The highest mortality rate observed in the BC Group was not due to increased pancreatic complication but from complications related to the clinical condition of the patient such as pneumonia and sepsis.

The lack of difference in organ conservation with respect to storage was evidenced by the absence of differences in the postoperative evolution (survival analysis and determining complications-conditions for a successful transplant) between the groups during a 3-month follow-up period.

The use of the Euro-Collins solution for organ storage is highly recommended because the solution is readily available, easy to manufacture, and with a cost that is 7 times lower than the Belzer solution and 18 times lower than the Celsior solution, leading to significant savings in pancreas transplants in Brazil. Our results indicate that the Euro-Collins solution results in cost reduction during the graft storage process without compromising the outcome of the transplants. Because a transplant is an expensive procedure, any cut in costs is relevant for the development of this modality, especially in developing countries. Further studies could confirm the findings reported here.

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