



CIRUGÍA y CIRUJANOS

Órgano de difusión científica de la Academia Mexicana de Cirugía
Fundada en 1933

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CLINICAL CASE

Routine hormonal therapy in the heart transplant donor[☆]



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Received 1 July 2014; accepted 27 January 2015

Available online 24 May 2016

KEYWORDS

Cardiac
transplantation;
Hormonal rescue;
Donor;
Levothyroxine

Abstract

Background: Successful heart transplantation depends largely on donor heart function. During brain death many hormonal changes occur. These events lead to the deterioration of the donor hearts. The 2002 Crystal Consensus advises the use of a triple hormonal scheme to rescue marginal cardiac organs.

Material and methods: A prospective, longitudinal study was conducted on potential donor hearts during the period 1 July 2011–31 May 2013. All donor hearts received a dual hormonal rescue scheme, with methylprednisolone 15 mg/kg IV and 200 mcg levothyroxine by the enteral route. There was at least a 4 h wait prior to the harvesting. The preload and afterload was optimised. The variables measured were: left ventricular ejection fraction cardiac graft recipient; immediate and delayed mortality.

Results: A total of 30 orthotopic heart transplants were performed, 11 female and 19 male patients, with age range between 19 and 63 years-old (Mean: 44.3, SD 12.92 years). The donor hearts were 7 female and 23 male, with age range between 15 and 45 years-old (mean 22.5, SD 7.3 years). Immediate mortality was 3.3%, 3.3% intermediate, and delayed 3.3%, with total 30 day-mortality of 10%. Month survival was 90%. The immediate graft left ventricular ejection fraction was 45%, 60% intermediate, and 68% delayed. The causes of death were: 1 primary graft dysfunction, one massive pulmonary embolism, and one due to nosocomial pneumonia.

[☆] Please cite this article as: Zetina-Tun H, Lezama-Urtecho C, Careaga-Reyna G. Terapia hormonal de rutina en el donador para trasplante cardiaco. Cir Cir. 2016;84:230–234.

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PALABRAS CLAVE

Trasplante cardiaco;
Rescate hormonal;
Donador;
Levotiroxina

Conclusion: It was concluded that the use of double rescue scheme hormonal therapy is useful for the recovery and preservation of the donor hearts. This scheme improves survival within the first 30 days after transplantation.

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Terapia hormonal de rutina en el donador para trasplante cardiaco**Resumen**

Antecedentes: El éxito de un trasplante cardiaco depende en gran parte de la función del corazón donado a que, durante la muerte cerebral ocurren cambios hormonales importantes y estos conducen al deterioro del órgano donado; por lo que el Consenso Cristal de 2002 recomienda el uso de triple esquema hormonal para el rescate de los órganos cardiacos marginales.

Material y métodos: Estudio prospectivo, longitudinal. Reunimos a potenciales donadores de corazón durante el periodo del 1 de julio del 2011 al 31 de mayo del 2013. Todos recibieron doble esquema de rescate hormonal, con metilprednisolona 15 mg/kg por vía intravenosa y levotiroxina 200 µg por vía enteral. Se esperó un lapso mínimo de 4 h antes de la procuración. Se optimizaron la precarga y poscarga. Se evaluaron: mortalidad del receptor y fracción de expulsión del ventrículo izquierdo, del injerto inmediata, mediata y tardía.

Resultados: Fueron realizados 30 trasplantes cardiacos ortotópicos, en 11 mujeres y 19 varones, con edad promedio: 44.3 ± 12.92 (rango 19-63 años). Los donadores de corazón, 7 mujeres y 23 hombres, con rangos de edad de 15 a 45 años (promedio 22.5 ± 7.3). La mortalidad inmediata fue del 3.3%, mediata 3.3% y tardía 3.3%. La sobrevida al mes fue del 90%. La fracción de expulsión del ventrículo izquierdo del injerto fue 45% inmediata, mediata 60% y tardía 68%. Las causas de mortalidad fueron: disfunción primaria del injerto (un caso), una tromboembolia pulmonar masiva y una neumonía nosocomial.

Conclusión: El uso de doble esquema de terapia de rescate hormonal es útil para la recuperación y la preservación del corazón y mejora la sobrevida dentro de los primeros 30 días postrasplante.

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Background

Since Dr. Christian Barnard¹ performed the first heart transplant in 1967, heart transplant success has lain in the control of acute or hyperacute rejection, and long term survival.² A key point in the control of these factors came about with the advent of calcineurin inhibitors in 1987.

A new challenge was simultaneously presented, upon which the success of a heart transplant outcome depends: primary graft dysfunction and sufficient assessment to obtain an optimum donor heart, mainly from marginal cardiac organs donated.

During brain death a number of hormonal, metabolic and systemic changes occur, including: the reduction of circulating thyroid hormones,³ the depletion of vasopressin reserves after 6 h,⁴ raised inflammatory response⁵ and the well known "adrenergic storm".^{6,7} All these hormonal, metabolic and systemic changes will lead to function deterioration of the donor heart, and to the increase in acute posterior rejection of the transplanted organ.⁸ Due to the above and since its acceptance in the 2002 Crystal Consensus, a triple hormonal scheme to rescue marginal donor cardiac organs⁹ has been

implemented and there have been many reports of increases of solid organs recuperated with the use of this scheme or algorithm.¹⁰

We are reporting our experience based on the Crystal Consensus scheme, with its modification, which consists in using it in all potential heart donors, with normal left ventricle ejection fraction, in a routine manner and not only in marginal transplants, as our main source of donors is distant procurements. We report its repercussion in immediate postoperative survival and the single use of a dual hormonal scheme with steroids and thyroid hormone by the enteral route through a nasogastric tube.

Material and methods

We conducted a prospective, longitudinal study which began on July 1, 2011 and terminated on May 31, 2013. All potential heart donors, aged between 15 and 45 and of both sexes were brought together. The potential donors were initially assessed using: anthropometry, electrocardiogram, echocardiogram (if available) and laboratory testing. If optimum

criteria were met for heart donation (in accordance with our protocol) and any other heart condition was ruled out, hormonal therapy administration was initiated with methylprednisolone 15 mg/kg intravenously (IV) by bolus injection and 200 mcg of levothyroxine in nasogastric tube with a repeated dose of the former drug, if needed, in 24 h. We waited a minimum of 2 h (ideally 6), after initiating standard hormonal therapy. We attempted to reduce the dose of the vasopressors, mainly of the noradrenalin, if it was being administered, and the procurement of the heart was made ideally within 6 h after the hormonal therapy. Open heart tertiary survey was made by the surgeon and this was the main guideline for obtaining procurement.

The variables measured were as follows: total ischaemic time, cardiopulmonary derivation time, recipient aortic clamping time, postoperative complications and primarily the survival of the procured organ in the immediate (first 24 h), intermediate (1st–7th day) and delayed (8th–30th day) postoperative period.

Statistical method: A descriptive statistical method was used to characterise the sample of this patient series.

Results

30 patients received transplants, 11 women (36.66%) and 19 men (63.33%) aged 44.3 ± 12.92 (19–63 years of age), with the following diagnoses as the causes of end-stage cardiac failure: idiopathic enlargement in 15 patients (50%), ischaemic cardiopathy in 13 (43.3%), restrictive in one patient (3.3%), Ebstein's disease in one case (3.3%). The functional class of the New York Heart Association (NYHA) was: III in eight patients (26.6%) and IV in 22 patients (73.3%).

All heart transplants performed were orthotopic, using the biatrial technique in 12 patients (40%) and bicaval technique in 18 patients (60%). Cardiopulmonary derivation time was 125.3 ± 26.34 min (range 69–196 min), total ischaemia time was 225.03 ± 61.13 min (119–366 min), aortic clamping of the "hot ischemia" receptor was 78.56 ± 12.62 min (55–109 min). The average difference in total ischaemia time and aortic clamping of the average receptor was 146.47 min.

Donor data were as follows: 7 women (23.3%), 23 men (76.6%), aged 22.5 ± 7.3 (range between 15 and 45 years of age).

Immediate mortality was 3.3% (one patient), intermediate 3.3% (one patient) and delayed 3.3% (one patient), with a total 30-day mortality of 10% (3 patients) and survival rate of 90% (27 patients).

The left ventricle ejection fraction prior to the heart procurement was on average 55%, obtained by echocardiogram in only 18 patients (90%). The left ventricle ejection fraction in the immediate postoperative period was an average of 45%, intermediate of 60% and delayed of 68%.

Complications presented were: acute kidney failure in 40% (12 patients) of whom 2 patients (6.6%) required kidney replacement therapy with continual veno-venous haemodiafiltration (Prisma®). Right cardiac failure of the organ presented in 6 patients (20%); sinus node dysfunction, in 6 patients (20%); delirium in 5 patients (16.6%); postoperative haemorrhaging in 2 patients (6.6%), and liver failure

in 2 patients (6.6%). One patient presented with pneumonia (3.3%), another with cerebral haemorrhaging (3.3%) and another with massive pulmonary thromboembolia (3.3%).

The cause of death in the immediate postoperative period of the one patient (3.3%) was primary graft dysfunction, in the intermediate period it was massive pulmonary embolism (3.3%) and in the case of delayed (3.3%) it was pneumonia and septic shock with positive culture testing of *Acinetobacter baumannii*. The mortality rate during the first 30 days was 10% (3 patients).

Discussion

Heart transplant is an undisputedly good option for end-stage heart failure and the success of a transplant is due to many factors. One of these is the ventricular function of the donated organ.^{11,12} During brain death a series of hormonal changes occur: antidiuretic or vasopressin levels drop, thyroid hormones are too low, blood interleukins increase, there is a change in the aerobic cycle in cells.⁴ In addition to this, during brain death "adrenergic storm" occurs whereby serum levels of noradrenaline are raised substantially, with devastating consequences on the potentially donated heart including: damage of the myocyte, increased in systolic and diastolic biventricular cardiac failure (predominantly right ventricle), arrhythmias, petechial haemorrhaging in the subendocardium, poorer endothelial functioning and loss of vasomotor tone, which induces a depression of potentially reversible myocardial contractibility.^{7,13}

All hormonal events led to the creation of the Crystal Consensus scheme for the use of hormones for rescue of potential marginal donated hearts, with excellent outcome.⁹ This scheme uses methylprednisolone at 15 mg/kg, triiodothyronine 4 µg U IV, vasopressin 1U IV and insulin 1U/h IV.^{14,15}

With the application of the hormonal Crystal Consensus rescue scheme, many authors have reported better recovery of hearts with ejection fraction of marginal left ventricle, lungs and kidneys and that a lower dose of vasopressors is required prior to procurement of thoracic organs.¹⁰

In this paper we modified the form of administration and the Crystal Consensus protocol. We used 2 hormonal drugs, methylprednisolone at 15 mg/kg IV bolus and levothyroxine 200 µg by the enteral route, instead of 3 or 4 hormonal drugs, like those of the protocol mentioned. Hormonal therapy was administered routinely, separately from the left ventricle fraction ejection found by echocardiogram during the first assessment and not as a rescue of marginal organ grafts with left ventricle ejection fraction under 40%. We waited at least 2 h (like in the Crystal Consensus protocol) after administration of the dual hormonal scheme for the expected effects and a maximum of 24 h. Final determination for obtaining the organ grafts for transplantation was decided by an objective assessment of the open heart cardiovascular surgeon.

Rosendale et al.¹⁵ in their work used 3 rescue hormones (steroids, thyroids and vasopressin), in addition to variable combinations of 2 of them and also individually. In this study we demonstrated that only the combination of the triple hormonal scheme (steroids, thyroid hormone and vasopressin) was greater than the combination of steroids

and thyroid hormones, both in the presentation of primary graft dysfunction (odds ratio of 0.45 vs. 0.66), mortality at one month (odds ratio of 0.47 vs. 0.67), and at 12 months 90% vs. 83.3%. The other dual or individual combinations had lower results, the combination of steroids and vasopressin IV being the poorest.

In our work we used steroids (methylprednisolone) and a thyroid hormone (levothyroxine) in a routine manner and our results were a mortality of 3.3% in the immediate post-operative period, 3.3% intermediate and 3.3% delayed, with a 10% total during the first postoperative month.

Left ventricle ejection fraction in our study was initially 45% and rose to 60% during the intermediate period, and improved in the delayed period to 65%. This was in accordance with the studies made by Berman et al.⁷ in which the recovery of the heart was presented between day 7 and 14, where it mimicked cardiac dysfunction suffered during brain death, subarachnoid haemorrhaging and Takotsubo syndrome for its similarity in adrenergic discharge, histopathological lesions, recuperation and non coronary lesions.

Thirty days mortality rate was 10%, but mortality attributed to primary dysfunction of the graft procured was 3.3%. This is important because graft dysfunction did not significantly present in the patients who received the standard dual hormonal therapy, providing an opportunity for better patient recovery with correct management.

Of the presented complications it is important to mention multifactorial acute kidney failure at a high percentage (40%). This high percentage is similar to that reported in medical literature.^{16,17} Right cardiac failure presented in 20% of patients but recuperation took place between 4 and 7 days, in accordance with that previously mentioned regarding left ventricle ejection fraction recovery.⁷

Total ischaemia time was 225.03 min (within the time ranges recommended by international guides, which is under 240 min¹⁸). The difference between total ischaemia and cold ischaemia time, or aortic clamping time of the receptor was 146.47 min, attributed to the transportation time from the place of organ origin. The latter was mostly a different origin from our centre. This was the reason why total ischaemia time was prolonged, as reported in the previous study by Careaga-Reyna et al.¹⁹

Our study consists of a small number of patients and if we take into consideration that a hospital which carries out 10–25 heart transplants yearly is considered to be of intermediate production on a worldwide level,²⁰ we believe it is an appropriate number and requires follow-up to assess the outcome at 6 months, and 1 and 5 years.

Conclusion

Hormonal rescue was created for the management of donated hearts with left ventricle ejection fraction ($\leq 40\%$). Based on the Crystal Consensus Scheme, we used hormonal rescue therapy in all heart donations, although their left ventricle ejection fraction was $\geq 50\%$. Using a dual hormonal rescue scheme with steroids (methylprednisolone 15 mg/kg/bolus IV) and thyroid hormones (levothyroxine 200 μ g by the enteral route), our group reached the following conclusions:

1. The possibilities of primary graft dysfunction and its association with mortality was lowered to 3.3%.
2. Mortality during the first 30 days fell to 10% in total.
3. Study control and follow-up over a longer period of 6, and 12 months is required.

Conflict of interest

The authors have no conflict of interests to declare.

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