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Original Article / Özgün Makale

The effect of donor ischemic time on mortality in heart transplanted patients

Kalp nakli hastalarında donör iskemi süresinin mortaliteye etkisi

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Background: This study aims to evaluate the effects of donor ischemic time on mortality in patients undergoing heart transplantation.

Methods: Between March 1998 and September 2012, 172 patients (135 males, 37 females; mean age 39.7±14.6 years; range 5 to 65 years) who underwent heart transplantation in our clinic were retrospectively reviewed. The patients were divided into two groups according to the graft ischemic time, including being equal or over 200 minutes (group 1) and under 200 minutes (group 2). The possible relationship between donor ischemic time and mortality was investigated during the early, mid, and long-term follow-up period.

Results: The mean donor age and follow-up were 29.9±11.8 years, and 1,295.0±1,249.1 days, respectively. The mean overall donor ischemic time was 181.7±61.2 min with 244.0±36.9 min in group 1 and 139.0±30.1 min in group 2. Although group 1 had higher intraoperative mortality rates (p=0.048), there was no statistical significance in postoperative mortality between two study groups. Each study group was divided into three subgroups with respect of donor age (≤25 years, 26-39 years, and ≥40 years) and no statistically significant difference was found in overall mortality rates among six study subgroups (p=0.307).

Conclusion: Improvements in myocardial protection and perioperative management procedures lead to increased survival rates in patients with heart transplantation. Donor heart preservation, operation procedures and the preoperative status of the recipients are considered more important risk factors on mortality after heart transplantation than donor ischemic time alone.

Keywords: Donor age; donor ischemic time; heart transplantation.

Amaç: Bu çalışmada kalp nakli yapılan hastalarda donör iskemi süresinin mortalite üzerindeki etkileri değerlendirildi.

Çalışma planı: Mart 1998 - Eylül 2012 tarihleri arasında kliniğimizde kalp nakli uygulanan 172 hasta (135 erkek, 37 kadın; ort. yaş 39.7±14.6 yıl; dağılım 5-65 yıl) retrospektif olarak incelendi. Hastalar greft iskemi süresinin 200 dakika ve üzeri olması (group 1) ya da 200 dakikanın altında olmasına (group 2) göre iki gruba ayrıldı. Donör iskemi süresi ile mortalite arasındaki muhtemel ilişki erken, orta ve geç takip dönemlerinde değerlendirildi.

Bulgular: Ortalama donör yaşı ve takip süresi sırasıyla 29.9±11.8 yıl ve 1295.0±1249.1 gün idi. Ortalama genel donör iskemi süresi 181.7±61.2 dk. olmakla birlikte, bu süre grup 1'de 244.0±36.9 dk., grup 2'de 139.0±30.1 dk. idi. Grup 1'de daha yüksek ameliyat sırası mortalite oranları saptanmasına rağmen (p=0.048), iki çalışma grubu arasında ameliyat sonrası mortalite açısından istatistiksel anlamlı bir fark saptanmadı. Çalışma gruplarının her biri donör yaşına göre (≤25 yıl, 26-39 yıl ve ≥40 yıl), altı alt gruba ayrıldı ve bu alt çalışma grupları arasında genel mortalite oranları açısından istatistiksel anlamlı bir farka rastlanmadı (p=0.307).

Sonuç: Miyokard koruması ve ameliyat sırası tedavi işlemlerdeki ilerlemeler, kalp nakli yapılan hastalarda sağkalım oranlarını artırmaktadır. Tek başına donör iskemi süresine kıyasla, donör kalp koruması, ameliyat teknikleri ve alıcıların ameliyat öncesi durumunun kalp nakli sonrası mortalite üzerine daha önemli risk faktörü olduğu düşünülmektedir.

Anahtar sözcükler: Donör yaşı; donör iskemi süresi; kalp nakli.

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The gradual increase in the number of both transplantation centers and patients on transplant waiting lists all over the world has forced heart transplantation teams to rethink the criteria for donor hearts due to the decrease in the candidate pool and increase in waiting list mortality rates. In addition to the diminishing number of brain death cases, a reduction of organ donations because of ethical or religious considerations has given rise to a decrease in local donor heart pools, so heart transplantation teams have started to harvest donor organs from more distant locations thanks to improvements in donor heart preservation methods that permit prolonged storage and the remote procurement of cardiac allografts.[1] As long as there are favorable survival rates for the recipients with allografts transplanted from far outside the generally accepted boundaries of donor age and ischemic time, transplantation teams will necessarily stretch the limits on the criteria for donor hearts. In the present study, we evaluated the effects of donor ischemic time and age on long-term mortality among patients who underwent heart transplantation in our clinic.

PATIENTS AND METHODS

The charts of 172 patients (135 males, 37 females; mean age 39.7±14.6 years; range 5 to 65 years) who underwent heart transplantation in our clinic between March 1998 and September 2012 were retrospectively reviewed in this study. The standard biatrial cuff technique was performed for orthotopic heart transplantation in all of the cases, and those who underwent both heart and lung transplantation were excluded from the study. The preoperative diagnosis was dilated cardiomyopathy in 125 patients (72.7%) and ischemic cardiomyopathy in 47 others (27.3%). Informed consent conforming to the tenets of the Declaration of Helsinki was obtained from each of the study participants.

To harvest the donor heart, the following procedure was performed. After the dissection of all donor organs except the heart, 30,000 U of heparin was administered for anticoagulation. In order to drain the blood into the right hemithorax and keep the pericardial cavity clearly visible, the right inferoposterior part of the pericardium was subsequently dissected. The superior vena cava (SVC) was then carefully tied and cut while paying attention to avoid any sinoatrial node damage. Afterwards, the inferior vena cava (IVC) and left superior pulmonary vein were cut in order to provide left and right heart decompression. After several heart beats, the aorta was cross-clamped, and one liter of the cold cardioplegic solution Plegisol™ (Abbott Laboratories, Abbott Park, IL, USA) was infused from the aortic root. In addition, topical cooling with cold isotonic saline was performed during this process.

After the completion of the cardioplegic solution infusion and development of complete cardiac arrest, the donor heart was immediately explanted. Donor ischemic time was defined as the time interval from the application of the donor aortic cross-clamp to the release of the recipient cross-clamp. The study population was divided into two groups, with group 1 being made up of those with a donor ischemic time of 200 minutes (n=70) or longer and group 2 comprised of those with a donor ischemic time of less than 200 minutes (n=102). The overall intraoperative and postoperative mortality rates of these two groups were then compared. The relationship between donor ischemic time and mortality was also evaluated at the end of the first, third, and sixth months and at the first- and fifth-year follow-ups. Furthermore, a comparison was also performed for the postoperative 10th year, which was defined as long-term mortality for the purpose of the study. Moreover, the relationship between the mortality rate and donor ischemic time in each of the two study groups was analyzed after they were divided into three subgroups, with subgroup 1 having donors of 25 years of age or younger, subgroup 2 having donors between 26 and 39 years old, and subgroup 3 having donors who were 40 years old or older.

The data was stored on a computerized database and analyzed using the SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). A chi-square test and Student's t-test were used in the statistical analyses, and a p value of below 0.05 was considered to be significant.

RESULTS

The mean donor age was 29.9±11.8 years, and the mean follow-up period was 1295.0±1249.1 days (range 1-4806). Furthermore, the overall average donor ischemic time was 181.7±61.2 minutes (range 90-410), but it was 244.0±36.6 minutes (range 200-410) for group 1 and 139.0±30.1 minutes (range 90-197) for group 2. Additionally, no statistically significant differences were determined with regard to mean patient age (p=0.322), gender (p=0.722), preoperative diagnosis (p=0.177), mean donor age (p=0.156), or mean follow-up time (p=0.849) between the two study groups. The demographic data is shown in Table 1.

The intraoperative mortality rate was 10% (n=7) in group 1 and 2% (n=2) in group 2. Although no

Table 1. Demographic data of the study participants

	Overall (n=172)			Group 1 (n=70)			Group 2 (n=102)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			39.7±14.6			38.4±15.3			40.6±14.0	0.322
Gender										
Female	37	21.5		16	22.9		21	20.6		0.722
Male	135	78.5		54	77.1		81	79.4		
Preoperative diagnosis										
DCMP	125	72.7		47	67.1		78	76.5		0.177
ICMP	47	27.3		23	32.9		24	23.5		
Donor age (years)			28.9±11.2			27.4±10.0			29.9±11.8	0.156
Donor ischemic time (min)			181.7±61.2			244.0±36.6			139.0±30.1	0.000
Follow-up (days)			1295.0±1249.1			1273.0±1258.4			1310.1±1248.8	0.849

SD: Standard deviation; DCMP: Dilated cardiomyopathy; ICMP: Ischemic cardiomyopathy.

statistically significant differences were present in the overall mortality rates between the groups (p=0.270), higher intraoperative mortality was found in group 1 (p=0.048). Higher survival rates were achieved in the patients in group 1, especially at the first, third, and sixth months and the first year of follow-up, but no statistically significant differences were found in the mortality rates at the end of the postoperative first month (n=172; p=0.421), third month (n=171; p=0.468), sixth month (n=168; p=0.607), first year (n=164; p=0.565), or fifth year (n=121; p=0.770). The long-term mortality rate of the 29 patients in group 1 was 86.2%, whereas it was 88.0% for the 50 patients in group 2 (p=0.817). The mortality rates for groups 1 and 2 are shown in Table 2.

The relationship between mortality and donor ischemic time was evaluated among the study participants with respect to donor age, with 82 recipients (47.7%) in subgroup 1 and 54 (31.4%), in subgroup 2, and 36 (20.9%) in subgroup 3. In addition, the overall mortality rates were 35.4%, 38.9%, and 55.6% in the three subgroups, respectively (p=0.115). Regarding donor ischemic time, no statistically significant differences were found in the mortality rates of any of the subgroups at the early-, mid-, and long-term follow-ups. The mortality rates of groups 1 and 2 by age are shown in Table 3.

In addition, we also divided the study population into six subgroups by donor age (≤25 years, 26-39 years, and ≥40 years) and donor ischemic time (<200 minutes and ≥200 minutes), but no statistically significant differences were noted in the overall mortality rates (p=0.307).

DISCUSSION

Several studies have been published that focused on the increased survival rates of patients who recently underwent heart transplantation. Some of these have studied the effects of donor age while others have concentrated on the donor ischemic time as it relates to survival in heart transplant cases. Because of the many incompatible studies involving different heart transplantation teams, the characteristics of an ideal donor organ have not yet been clearly defined. A maximum of 360 minutes of donor ischemic time is known to be optimal for heart transplantation, and graft dysfunction in connection with excessive ischemic time has been reported due to the disruption

Table 2. Mortality rates of the study participants

	Overall (n=172)		Group 1		Group 2		
	n	%	n	%	n	%	*p*
Intraoperative (n=172)	9	5.2	7	10.0	2	2.0	0.048
Postoperative 1st month (n=172)	25	14.5	12	17.1	13	12.7	0.421
Postoperative 3rd month (n=171)	35	20.5	16	23.2	19	18.6	0.468
Postoperative 6th month (n=168)	41	24.4	18	26.5	23	23.0	0.607
Postoperative 1st year (n=164)	45	27.4	20	29.9	25	25.8	0.565
Postoperative 5th year (n=121)	65	53.7	25	52.1	40	54.8	0.770
Postoperative 10th year (n=79)	69	87.3	25	86.2	44	88.0	0.817

Table 3. Mortality rates between the two study groups with respect to donor age

	Mortality				
	Group 1		Group 2		
	n	%	n	%	*p*
Postoperative 1st month (n=172)					
Donor age					
≤25 years (n=82)	6	16.2	3	6.7	0.169
26-39 years (n=54)	2	9.1	4	12.5	0.695
≥40 years (n=36)	4	36.4	6	24.0	0.446
Postoperative 3rd month (n=171)					
Donor age					
≤25 years (n=81)	8	22.2	6	13.3	0.293
26-39 years (n=54)	4	18.2	6	18.8	0.958
≥40 years (n=36)	4	36.4	7	28.0	0.616
Postoperative 6th month (n=168)					
Donor age					
≤25 years (n=81)	10	27.8	8	17.8	0.282
26-39 years (n=51)	4	19.0	6	20.0	0.933
≥40 years (n=36)	4	36.4	9	36.0	0.983
Postoperative 1st year (n=164)					
Donor age					
≤25 years (n=77)	11	31.4	9	21.4	0.319
26-39 years (n=51)	5	23.8	7	23.3	0.969
≥40 years (n=36)	4	36.4	9	36.0	0.983
Postoperative 5th year (n=121)					
Donor age					
≤25 years (n=51)	13	56.5	15	53.6	0.833
26-39 years (n=40)	8	47.1	12	52.2	0.749
≥40 years (n=30)	4	50.0	13	59.1	0.657
Postoperative 10th year (n=79)					
Donor age					
≤25 years (n=32)	13	81.2	16	100	0.069
26-39 years (n=25)	8	88.9	13	81.2	0.617
≥40 years (n=22)	4	100	15	83.3	0.380

of needs and the consumption of the donor organ.[2-4] While cold storage during transport is an effective and frequently used method in the preservation of the donor heart, the content of the storage solution is another important factor. Although hypothermia is widely used to preserve these organs during transport, the potential risks of induced crystallization and congelation at 0 °C have to be kept in mind; hence, cold storage of a donor heart at under +3 °C is not recommended.[5]

Additionally, the prolonged donor ischemic time is primarily related to the harvesting of allografts from more distant locations. Difficulty dissecting cardiac and mediastinal structures in patients with ventricular assist device (VAD) is another reason for longer graft ischemic time. The International Society for Heart and Lung Transplantation (ISHLT) has issued reports which show the negative effect that increased donor ischemic time has on mortality within the first year of heart transplantation.[6,7] Graft dysfunction due to prolonged donor ischemic time, which may lead to an increased need for inotropic agents as well as postoperative VAD implantation, has not only been linked to mortality but has also been connected with a decrease in the early postoperative functional capacity of recipients.[8] Several studies have also reported reduced survival rates in patients with prolonged donor ischemic time,[4,6,9-11] but other studies have not shown any connection.[1,12,13] Kilic et al.[11] studied 9,404 patients who underwent an orthotopic heart transplantation from 1987 to 1999 and concluded that younger patient age (<55 years), a shorter donor ischemic time, and younger donor age were the most

important factors for predicting the 10-year survival rate after cardiac transplantation. In addition, they also concluded that being Caucasian was also a significant factor. The correlation between donor ischemic time and survival rates, especially in short-term follow-ups, has been stated in various publications.[1,4,14,15] Although we found a higher intraoperative mortality in the cases with a donor ischemic time of ≥200 minutes (p=0.048), there were no statistically significant differences in the postoperative early-, mid-, and long-term mortality rates between groups 1 and 2 in our study.

Özatik et al.[16] reported that except for donor age, none of the other parameters, including cross-clamp time, donor gender, recipient gender, pulmonary artery pressure (PAP), preoperative EF, donor ischemic time, and donor-recipient gender, had a statistical impact on general survival rates. They also found 10-year survival rates of 22% for donor recipients who were over the age of 25 and 75% for those who were 25 years old or younger. Russo et al.[17] also determined that younger donor hearts had an increased tolerance toward ischemia. Furthermore, in a previously published study from our center, the mean donor ischemic time and donor age were 184.9 minutes and 28.1 years in the surviving 73 recipients; whereas these parameters were 164.5 minutes and 31.5 years in the 50 patients who died during the follow-up period (p=0.1 and p=0.13, respectively).[18] In this study, the overall mortality rates were 35.4%, 38.9%, and 55.6% in subgroups 1, 2, and 3, respectively (p=0.115). Moreover, when we made a comparison involving the six subgroups, we discovered a tendency toward higher mortality rates in donor recipients who were 25 years or younger with a donor ischemic time of ≥200 minutes until the postoperative fifth year. The same tendency was also realized in those aged 40 and older with a donor ischemic time of ≥200 minutes until the sixth month of postoperative follow-up. However, no statistically significant differences between mortality and donor ischemic time with respect to donor age were identified in any of the subgroup analyses, which could be the result of the rigorous examination of the harvested allografts from more remote locations.

Conclusion

Advances in myocardial protection and perioperative surgical procedures have improved the survival rates of patients who undergo heart transplantation. Donor tissue damage is determined by surgical technique as well as by graft preservation during harvesting, transport, and implantation. The optimal preparation and storage of grafts from remote locations may yield the best postoperative results, even when they are harvested from older donors. Therefore, we believe that our findings indicate that donor heart preservation and operation procedures as well as the preoperative status of the recipient should be considered as more important risk factors for mortality after heart transplantation than donor ischemic time.

Declaration of conflicting interests

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