Nephrology, Dialysis and Transplantation News

Expanding the donor pool to increase renal transplantation

Bernard Cohen1, Jacqueline M. Smits1, Bernadette Haase2, Guido Persijn1, Yves Vanrenterghem3 and Ulrich Frei4

1Eurotransplant International Foundation, 2Dutch Transplantation Foundation, Leiden, The Netherlands, 3UZ Gasthuisberg, Nephrology, Leuven, Belgium and 4Humboldt Universität zu Berlin, Charité Campus-Virchow-Klinikum, Berlin, Germany

Abstract

Introduction. The goal of the Eurotransplant renal allocation scheme is to provide every patient on the waiting list with a reasonably balanced opportunity for a donor offer. New initiatives were taken in order to maximize donor usage while maintaining a successful transplant outcome.

Methods. Two Eurotransplant projects were launched in order to accommodate changes in donor and recipient profiles. A re-addressing of the non-heart-beating donor pool was undertaken and an allocation scheme in which organs from donors aged >65 are allocated to recipients aged >65 [the Eurotransplant Senior Programme (ESP)] was introduced.

Results. Especially in The Netherlands, an enormous increase in the number of non-heart-beating donor kidneys has been observed, however with a pacekeeping reduction in heart-beating donors. The organization-wide implementation of the ESP has been successful. The 3 year graft survival rates for these age-matched transplants were as good as the human leukocyte antigen (HLA)-matched transplants (64 vs 67%) (P = 0.4).

Conclusion. Within the framework of sound research, the utmost flexibility and creativity is needed to keep or even increase the number of renal transplants when faced with a quantitatively stagnating but qualitatively deteriorating donor pool. Both the non-heart-beating donor protocol and the ESP have proven to be quite successful in achieving this goal without compromising the outcome for the individual end-stage renal disease patient.

Keywords: expanded criteria donors; non-heart-beating donors; renal allocation

Introduction

Transplantation provides benefits to society as a whole as well as to the individuals who receive transplants. It is often the most cost-effective form of treatment for end-stage disease patients and offers the opportunity for patients disabled by illness to play a fuller and more active role in society, thus reducing the costs of health care and social care [1].

However, this form of treatment is limited by the availability of human organs suitable for transplant. In part, the shortage is the result of the success of transplantation and the consequent increase in potential transplant recipients.

Changes in donor demographics also contribute to persistently low numbers of donor organs [2]. The ideal donor is someone aged between 16 and 45, who dies as a result of cerebral trauma often caused by a road traffic accident. However, this profile does not fit the average donor in 2004. Potential donors currently are more likely to be older than in previous years and are more likely to have died following a stroke than cerebral trauma [3,4]. In addition, graft survival rates for organs from these donors are significantly worse than from younger donors dying from trauma [3,5,6].

Three year graft survival rates for renal allografts from donors whose cause of death was cerebral trauma were 86 and 79% for donors aged <55 and >55, respectively (P = 0.03). Renal graft outcome rates at 3 years for allografts from donors whose cause of death was a cerebrovascular accident (CVA) were 85 and 72% for donors aged <55 and >55, respectively (P = 0.0001) [2].

As the population ages, more and more older patients are entered onto transplant waiting lists, thus increasing pressure on transplant programmes with respect to waiting list management. Figure 1 shows that the number of renal recipients in the age category of >65 years more than doubled in the past 10 years. The average number of recipients in the age group 60–65 increased by 37% from 1999 to 2003.
(average 595) as compared with the period from 1994 to 1998 (average 433). If all potential transplant recipients are to be treated in an equitable way, there is no room for discrimination on the grounds of age or social worth, although most clinicians would probably prefer to allocate organs to those with the longest potential life span [7]. Thus, the transplant community, which is under a moral obligation to make the best possible use of donated organs, is faced with a dilemma: how to balance the needs of the potential recipient with the need to allocate organs fairly [8]. For older end-stage renal disease (ESRD) patients on the waiting list, this balance is even more difficult to achieve as these patients compared with patients under 50 have a five times greater likelihood of dying while waiting for a donor kidney [9].

Organ allocation

In simple terms, Eurotransplant attempts to identify the best recipient for each available donor organ (Table 1) [Eurotransplant is responsible for the mediation and allocation of all organs in Austria, Belgium, Germany, Luxembourg, The Netherlands and Slovenia (www.eurotransplant.nl)]. In reality, this decision is not that simple and a balance must be achieved between optimal use of all available organs, including those from marginal donors such as the elderly, and optimal life expectancy of all transplant candidates. In the day-to-day reality of organ allocation and in the face of donor shortages, this can mean achieving maximal transplant outcome under marginal conditions.

Allocation algorithms that take into account factors such as age, human leukocyte antigen (HLA) match, waiting time and clinical urgency have been developed using computer models based on sound outcome data and scientific evidence [10]. Such allocation algorithms are, by necessity, not set in stone. Rather, they are flexible schemes that can be altered to accommodate, for example, changes in donor or recipient profiles and the latest outcome data. The structure of Eurotransplant and its decision-making process allow for changes to be made to the allocation algorithm based on scientific data. In order to make such changes, each organ-specific advisory committee must submit its recommendations to the Eurotransplant Board. The Board makes the final decision to accept or refuse the proposed change to the algorithm.

Expanding the donor pool

As a result of fewer road traffic accidents, and improved intensive care facilities, donors are more likely to have died as the result of a stroke rather than cerebral trauma [2], hence the donor pool has changed qualitatively. In addition, the transplant community is faced with an increasing donor shortage. Therefore,
ways to expand the donor pool have been sought and the reasons for rejecting donors have come under close scrutiny. The worldwide trend is now to identify suboptimal donor populations, such as donors aged over 65 years [2–6,10] or to introduce new initiatives such as the use of asystolic, or non-heart-beating, donors. In the latter protocol, organs are procured when the heart and thus the circulation of the donor has come to a standstill. Wijnen et al. have greatly contributed to widen the acceptance of the revival of this old procedure [11]. Before the concept of brain death became sufficiently accepted, non-heart-beating donors were the only source of organs.

Non-heart-beating donors

Publications in the mid-1990s revealed that transplant survival with kidneys from non-heart-beating donors was similar to that of transplants with kidneys from heart-beating donors [11]. These encouraging results will undoubtedly lead to an increased number of transplant centres introducing a non-heart-beating donor protocol. The potential contribution of this category of donors to the pool remains the subject of debate, but may be considered to be substantial [12,13]. For example, in the USA, it is estimated that the use of non-heart-beating kidneys could increase the supply of kidney transplants by a factor of 2–4.5 [14]. In practice, most recent data revealed that only some 200 of such donors were actually reported to organ procurement agencies in the USA. Thus, the notion of more donors becoming available through non-heart-beating donation still remains to be proven (Table 2).

In contrast, within Eurotransplant, The Netherlands in the past decade has seen the opposite development. A remarkable increase in the number of non-heart-beating kidney transplants was noticed (Figure 2). Simultaneously, the number of traditional heart-beating kidney transplants has diminished at the same rate. Surprisingly, each annual increase in non-heart-beating donations has been offset by a similar decreased rate in heart-beating donors. As seen from Figure 2, the total number of annual renal transplants from deceased donors has remained the same over the past decade. However, it should also be noted that by nature, non-heart-beating donors do not yield as many other organs besides kidneys as seen with traditional heart-beating donors. It is very tempting to postulate that no new donor source is being used, but simply that a procedural shift has taken place. In other words, could it be that these non-heart-beating donors were the heart-beating donors for whom initially no consent was obtained? Although this speculation cannot (yet) be substantiated by facts, our theory is supported by a trend very similar to the one described above in the UK, albeit less marked (Sue Sutherland, CEO, UK Transplant, personal communication July 2004).

What about non-heart-beating donations in the other Eurotransplant countries? For Germany, the answer is brief: by law, such donations are prohibited, as well as transplantation of organs from non-heart-beating donors originating from other countries. Austria had only very few of these donors in the past few years, and in Belgium, interest in exploring this possibility has only arisen recently. Apparently, the availability in these two countries of approximately twice as many organ donors as compared with most other European countries has contributed to this relatively low activity level. It should be noted, however, that presumed consent legislation potentially can lead to a rapid increase in this category of donors in the near future.

Until recently, it was accepted wisdom that as organs lose functional capacity with age, organs from older donors would not be suitable for transplant. However, studies now suggest that the chronological age of a donor does not necessarily give an indication of the condition of that person’s organs. Provided that transplant conditions are optimized, organs from older donors can survive as long as organs from other donors [15,16]. Moreover, while a kidney that is functioning at less than its peak physiological capacity may not be the best solution for a young patient on dialysis, it may be suitable for an older patient with a shorter life expectancy.

Improvements in immunosuppressive strategies and organ preservation techniques in recent years have also increased the chances of success for such transplants. Studies in the USA and Spain demonstrated that while kidney transplants from older people do carry a greater risk of reduced survival and poorer renal function than those from younger donors, excellent outcome could be achieved with a combination of careful donor and recipient selection, good surgical and organ preservation techniques and, if necessary, transplant of both donor kidneys into a single recipient [15–17].

Table 2. Non-heart-beating donors after cardiac arrest (type III): ‘ventilator switch-off’ procedure

<table>
<thead>
<tr>
<th>Year</th>
<th>USA (291 × 10^6 inhabitants)</th>
<th>The Netherlands (16 × 10^6 inhabitants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>169</td>
<td>53</td>
</tr>
<tr>
<td>2002</td>
<td>191</td>
<td>57</td>
</tr>
<tr>
<td>2003</td>
<td>268</td>
<td>94</td>
</tr>
</tbody>
</table>

Data source: USA, AOPA/UNOS; The Netherlands, Dutch Transplantation Foundation.
graft has a greater chance of surviving an older than a younger recipient.

Thus, Eurotransplant developed the ESP, an allocation scheme solely based on the concept of matching between metabolic demand of the graft recipient and excretory capacity of the donor organ [18]. The rationale for a donor to recipient age matching policy in which a kidney graft should outlive the recipient implied that HLA matching was disregarded in assigning donor organs.

However, the use of organs from elderly donors is often accompanied by increased incidences of delayed graft function and rejection [19]. To guarantee an acceptable degree of success, defined as graft viability, strict rules for participating centres within the Eurotransplant region initially were imposed: (i) to reduce ischaemic damage, kidneys should be transplanted with the shortest possible cold ischaemia time; and (ii) to reduce immunological risk, only non-immunized [i.e. panel-reactive antibody (PRA) < 5%] first transplant recipients were included.

The ESP allocation scheme furthermore included the option of transplanting both kidneys to a single recipient in cases in which the donor creatinine clearance was <70 ml/min.

Tailor-made allocation schemes like ESP are designed by Eurotransplant and offered thereafter to the Eurotransplant community. Thus, treating physicians in individual centres have the responsibility to carry out the details of the programme and to obtain informed consent from their patients.

After 3 years, 64 and 67%, respectively, of ESP and control grafts survived \(P = 0.4\) (Figure 3). When losses of grafts as a result of patient death were censored, survival rates in each group were 70 and 71%, respectively \(P = 0.8\) (Figure 4). Follow-up data were available for no less than 95% of the transplants.

Especially for the ESP transplants, initial renal function is important for long-term graft outcome. Figure 5 shows that ESP and control transplants with a good initial function yielded a 3 year graft survival rate of 76 and 79\%, compared with 54 and 70\%, respectively, for ESP and control transplants with a delayed graft function. While censoring for death with a functioning graft, these rates were 81 and 85\%, and 62 and 73\%, respectively (Figure 6).

These 3 year data show that there was no difference between patients who received grafts from elderly donors via ESP and those who received similar kidneys via the usual HLA-driven allocation procedure. These data suggest that, if care is taken to avoid the accumulation of additional risk factors such as long cold ischaemic time and retransplantation, an old-for-old allocation scheme can be operated successfully.

It should be emphasized that the ESP protocol does not set any restrictions on the co-morbidity pattern for these old ESRD patients. Moreover, special pre-renal transplant interventions, such as coronary artery bypass graft (CABG), are not mandatory. This leads to an enormous discrepancy in disease severity between ESP transplant candidates in one centre vs another [19]. Post-transplant outcome results in an individual centre may therefore differ from the overall Eurotransplant outcome.

With programmes such as ESP, elderly patients will have a more equitable chance of transplantation. In the past, elderly recipients were omitted from waiting lists because of the shortage of organs and because of their increased vulnerability to peri-operative
complications with consequently lower success rates [20]. ESP not only offers these patients a chance of receiving a transplant, but also allows for the best possible transplant conditions as imposed by the protocol, such as short cold ischemic period (CIP) and strict patient inclusion criteria.

As shown in Figure 1, there is a significant increase in the number of elderly renal transplant recipients being reported to the Eurotransplant waiting list. Apparently, the success of ESP has encouraged referring nephrologists to offer renal transplantation to elderly patients as well. Additionally, an increased usage of elderly donor kidneys has been reported over the past years. Prior to ESP, 10% of all used donor kidneys were retrieved from donors over 65 years of age. Since the implementation of ESP, this proportion has increased to 14.2% (Figure 7).

Fig. 3. Graft survival rates for ESP kidney transplants and control kidney transplants 1999–2002.

Fig. 4. Graft survival rates for ESP kidney transplants and control kidney transplants 1999–2002 censored for death with a functioning graft.
Discussion

The continuing shortage of human donor organs has encouraged the transplant community to look carefully at the restrictions previously placed on potential donors. In addition, they have also been forced to check the validity of these restrictions. New initiatives such as non-heart-beating donations and the use of elderly donors are the most significant recent developments to increase the availability of donor organs. Obviously, non-heart-beating donations have not yet yielded the originally predicted increase in organ availability and may in fact jeopardize the practice of reporting heart-beating donors, providing multiple organs for transplantation. Only when the contribution of this category of donors leads to an increase in the

---

Fig. 5. Graft survival rates for ESP and control kidney transplants with an initial delayed graft function 1999–2002.

Fig. 6. Post-transplant survival rates for ESP and control transplants, stratified for initial function or delayed graft function 1999–2002 censored for death with a functioning graft.
total number of kidneys available—and not to a ‘substitution’—should its potential be considered. The use of kidneys from elderly donors was thought to be an option with a suboptimal outcome. However, the evidence suggests that kidneys from older donors, even those with a slightly reduced functional capacity, appear to do well in both older and younger patients [18,19]. It therefore seems likely that other factors, such as those relating to the recipient, may be more influential on the final outcome than donor kidney quality alone. Nevertheless, the outcome from transplants in older people should be optimized, for example, by reducing the cold ischaemia time and/or by using a double kidney transplant [16,18].

However, as the clinical needs of patients must be constantly weighed against the need to allocate organs in an equitable way, restrictions must be lifted with caution and only on the basis of sound scientific research. The decision to use kidneys from donors aged 65 years or more may increase the pool of donors, but it may also increase the risk for individual patients.

Allocation algorithms employed by organ exchange organizations such as Eurotransplant need to be updated regularly to take into account developments such as the use of suboptimal donor organs. If they are not modified, organs will not be allocated in the fairest possible way. Even so, no single allocation algorithm will be accepted by the entire transplant community and there will always be objections to the criteria on which they are based. Objections are inevitable but, within a democratic system, they can be minimized or overcome.

Eurotransplant has responded to the continuing shortage of organ donors and the changing characteristics of donors by adapting its kidney allocation algorithm to include donors aged 65 years or more in ESP. Data from ESP in conjunction with data from other studies suggest that there is a good chance of maximizing outcomes provided that transplant conditions are optimized and donor and recipient are carefully selected.

Acknowledgements. The cooperation of all clinicians and data administrators in all Eurotransplant centres is gratefully acknowledged; without their ongoing efforts in providing data to the registry, this study could not have been performed. We would like to acknowledge the support of Mike Smith from Eurotransplant and Monique Sieber from the Dutch Transplantation Foundation who have provided all the data and tables for this report.

Conflict of interest statement. None declared.

References

Received for publication: 5.3.04
Accepted in revised form: 31.8.04