Results of transplantation of kidneys from expanded criteria donors

Kidney transplantation is a renowned method of renal replacement therapy and it enables to achieve better short-term and long-term survival outcomes compared to chronic dialysis therapy. Due to deficiency of organs available for transplantation, organs from expanded criteria donors (ECD) are used more and more often.

Objective of the work: The work aimed to compare results of transplantation of kidneys from standard donors (SCD) and expanded criteria donors (ECD).

Material and methods: The analysis included 232 patients who received kidneys from deceased donors, in the period 2010-2011 at the Chair and Department of General and Transplantation Surgery, Warsaw Medical University. Recipients were divided into 2 groups: SCD(n=176) and ECD(n=76). Recipients in both groups did not differ with regard to the age, sex, dialysis therapy duration prior to transplantation, immunosuppression or immunocompatibility with donors. Graft survival, recipient survival, delayed graft function (DGF), eGFR, blood creatinine levels and number of acute rejection (AR) episodes were analysed.

Results: There were no statistical differences with regard to one-year graft survival rate between study groups: 87.5% in the ECD group vs. 92.3% in the SCD group, one-year recipient survival rate: 95.2% vs. 98.6% for ECD and SCD, respectively, DGF was significantly more common in the ECD group– 56.2% vs. 34.5% in the SCD group (p<0.05), eGFR in the SCD group was higher compared to ECD: 51.7 mL/min/1.73m².
Kidney transplantation is an optimum method of treating end stage renal disease. Patients receiving haemodialysis (HD) are at a risk of diseases associated with renal dysfunction itself, as well as with dialysis therapy, and at a higher risk of death above all. Pursuant to European multi-centre studies the expected survival rate for patients receiving dialysis therapy for more than 5 years is below 50% and it is below 30% for patients receiving dialysis therapy for more than 8 years (1). Social or occupational isolation is not unimportant, and it has a negative effect on the mental and emotional status of patients (2). The quality of life of patients with a normally functioning transplanted kidney is much better compared to the one of patients receiving dialysis therapy, irrespective of a dialysis type (3, 4). Assuming that dialysis duration is 3.5 hours, time to go to and back from a centre is 2 hours, and the procedure is performed 3 times a week, patients waste about a month in a year for dialysis therapy. As a result of kidney transplantation, patients with end-stage renal failure have a chance to minimise negative aspects of this disease and to go back to normal life style and social functions. What is more, an economical aspect also favours kidney transplantation. As early as within the first year costs of transplantation are lower compared to dialysis therapy, and with each year when the graft is functional this difference becomes bigger. The balance does not include costs of sick leaves, hospitalisation due to complications, benefits and disability pensions for patients receiving dialysis therapy. A large proportion of patients who received kidney transplants regain full professional activity and in this way they pay back the costs of treatment (5, 6, 7). Based on data presented by Poltransplant in 2013 it can be concluded that the mean waiting time for kidney transplantation since a patient was enlisted on the NWL is 10 months, whereas it is 2 years and 6 months since the start of dialysis therapy. In 2013, 2% of patients from the list who awaited transplantation died. A disproportion between the number of organs for transplantation and the number of recipients is a significant problem of transplantation medicine. It is a challenge to transplantation specialists. Methods that might help solve this problem include: improvement of deceased donor referral rates, popularisation of the idea of living donor kidney transplants, wider use of organs from expanded criteria donors (ECD), optimised allocation of collected organs. Due to higher acceptance of organs from ECD, the age of real organ donors has a growing tendency (8). Pursuant to the data presented by Poltransplant, a share of organ donors aged 51 - 65 years and older than 65 years is constantly increasing in the group of all donors (8). The main cause of death of donors in Poland in the period 2006-2013 was a cerebrovascular incident (haemorrhagic or ischaemic stroke), followed by craniocerebral trauma (8). When such data as age and cause of death are analysed, it turns out that expanded criteria donors are creating the group, which is constantly growing. However, the use of kidneys from expanded criteria donors is associated with slightly poorer remote outcomes, but it is a solution more beneficial to patients compared to continued haemodialysis therapy (11, 12).

The aim of this study was to compare results of transplantation of kidneys from standard criteria donors (SCD) and expanded criteria donors (ECD).

**PATIENTS AND METHODS**

Between January 2010 and December 2011, 262 kidney transplantations were performed in our center. Kidneys were procured from living related donors – LRD (22/262; 8.4%) and deceased donors – DD (240/262; 91.6%). Two hundred twenty DD kidneys were kept in LifePort (Organ Recovery, Itasca, IL, USA) or MOX-100 (Waters Instruments, Rochester, MN, USA) machine perfusion prior to transplantation. The remaining 20 DD kidneys were kept in cold storage.

DD data (type of donor – ECD or SCD, and time of ICU stay) as well as data about surgical procedure (time of procedure - from skin incision till skin stitches have been done, CIT) and recipient data [age, human leukocyte antigen (HLA) mismatch, immunosuppression treatment, BMI, occurrence of DGF, number of HD sessions post-transplantation, AR occurrence, renal function up to 12 months post transplantation (creatinine level, return to HD treatment) comorbidities] were retrospectively collected.

**Expanded Criteria Donor** was defined according to definition by Organ Procurement and Transplantation Network (OPTN) / United Network for Organ Sharing (UNOS) (9, 10). As ECD donors were qualified all donors aged 60 years old or older, or 50 years old or older with at least two out of three following conditions: history of arterial hypertension, serum creatinine levels >1.5 mg/dL, cause of death from a cerebrovascular incident. All others donors were SCD.
Data were obtained from 76 patients who received kidneys from ECD group and 156 patients who received kidneys from SCD group.

**Delayed graft function (DGF)** was recognized as a need for dialysis in the short (7 days) period after kidney transplantation regardless of reason (hyperkalemia, high serum urea concentration, hyerhydration). **Primary Non-Function (PNF)** was defined as permanent loss of graft function immediately after transplantation. **Acute rejection (AR)** was biopsy proven and diagnosed according to Banff 2009 criteria. **Cold Ischemia Time (CIT)** was measured since start of in situ perfusion till start of vascular anastomosis.

**Immunosuppression protocol**

All kidney recipients were prescribed triple drug immunosuppression protocol consisted of calcineurin inhibitors (tacrolimus or cyclosporine) combined with prednisolone and mycophenolate mofetil or mycophenolate sodium. Tacrolimus or cyclosporine was administered at 0.2 mg/kg or 10 mg/kg per day, respectively, starting with a half-dose on the day of transplantation with individually-adjusted doses based on tested blood levels. Mycophenolate mofetil or mycophenolate sodium were administered twice a day in 1.0g or 720mg doses intravenous prednisolone was given on the operative day: 250 mg during anastomoses and 125 mg over 12-24 h. Twenty milligrams prednisolone was given orally on the third post-operative day, followed by a decrease to 10-15 mg by the end of the month. Induction immunosuppression (basiliximab or thymoglobulin) was administered in cases of second transplantation, panel reactive antibodies (PRA) above 20%, 4 or more mismatches.

**Statistical Analysis**

Categorical variables of the two patient groups were compared using Chi-square or Fisher’s exact tests. Student’s t-tests or Wilcoxon tests were applied for testing differences between means or medians, respectively. A critical level for hypothesis testing was set at 0.05. The statistical software Statistica 10.0 (Statsoft, Tulsa, OK, USA) was used for analysis.

**RESULTS**

Kidneys in ECD group were retrieved from 43 DD and from 85 DD in SCD group. Data of donors demographic within the groups is in table 1. Ninety-one per cent of kidneys transplanted in ECD group and ninety of SCD kidneys were perfused with machine perfusion (p=NS) prior to transplantation. CIT was slightly but significantly longer in ECD group – 31.4 +/- 8 hours versus 28.7 +/- 8 hours in SCD group (p=0.02). Recipients from ECD group were slightly but significantly older with higher BMI and more often with ischemic heart disease diagnosed prior to transplantation (tab. 2). There were no difference according to HLA mismatch, immunosuppression treatment after transplantation (tab. 2).

DGF was more often observed in ECD group (Fig.1). Episodes of AR did not differ between the groups (tab. 2). One-year patients and graft survival did not differ between the groups (Fig. 2). Mean creatinine level up to one year did not differ between the groups (Fig. 3) although mean creatinine clearance was significantly better in SCD group (tab. 2) one-year post transplantation.

**DISCUSSION**

**Delayed graft function (DGF)**

In the material from our centre, DGF was significantly more frequently observed in the ECD group: 56.2% vs. 34.5% in the SCD group (p< 0.05). Many analyses indicate that DGF is significantly more frequently observed in a group of recipients of kidneys from ECD compared to recipients of kidneys from SCD. DGF is a factor unfavourably affecting graft survival in case of kidneys from ECD and SCD - it is a conclusion of a paper published by Nassima Smail et al. (13). Ramalho et al. did not report a negative correlation between DGF and outcomes of kidney transplantation, and its rate in both groups: ECD and SCD was the same (14). Fraser et al. observed that the DGF rate in the SCD group was lower (21.7% vs. 37.6%), and in a 5-year follow-up it affected the graft survival rate. It reduced its survival rate by 9%. In the ECD group the incidence of DGF is higher, but it does not affect the 5-year survival rate. It suggests that DGF has no evident effect on the outcomes of kidney transplantation (15). Collini et al. presents less favourable results regarding the survival rate of patients after transplantation of kidneys from ECD and ECD graft survival in 1-, 2- and 3-year follow-up (16). Italian researchers, Pretagostini et al. conducted an analysis with 121 patients (ECD =46, SCD=75). They reported higher incidence of DGF in the ECD group. The authors determined that the donor age 60 years and CIT >15 hours are factors tightly associated with this phenomenon (17). Kim SM at al. reported that shortening of CIT is of great importance. In both study groups, ECD vs SCD, the rate of DGF was similar. It was demonstrated that shortening of CIT positively affects transplantation outcomes. In a Korean centre it is possible to shorten CIT to minimum as a distance to transport a donated organ to a centre is short. Transplantation procedures are performed in three centres. Organ donation and transplantation is performed at the same centre. The organ donation procedure starts only when a recipient has been selected and prepared for transplantation. Additionally, a rule that recipients and donors should be of similar age is used. The authors claim it shortens time necessary for a recipient to give their consent for transplantation of kidney from an expanded criteria donor. In a Korean centre CIT was 3.6 h +/- 1.2 h. The authors report that CIT for kidneys from the ECD
group was longer only in 3 cases (however, it did not exceed 9 h) (18). Johnston et al. also emphasise the significance of CIT on the outcomes of transplantation of kidneys from ECD. Researchers observed that the incidence of PNF, DGF in the ECD group for CIT<8 h is comparable to SCD at CIT<20 h (19). Spanish researchers compared a group of recipients of ECD kidneys (where CIT 9.3h +/- 2.5h, n=24) with SCD kidneys (where CIT 8.4h +/- 3.3h, n=50). They did not observe significant differences with regard to PNF, DGF, AR and graft survival in a 12-month follow-up. However, a lower GFR value was observed in the ECD group (20). As a result of shortening of CIT and decreased organ damage associated with organ preservation it is possible to obtain similar results in the ECD and SCD groups; however, the function of ECD kidneys is slightly poorer (21). Saidi et al. performed an interesting analysis as they assessed renal and economical parameters comparing kidneys from ECD, from donors after irreversible cardiac arrest and SCD. The analysis includes 271 transplanted kidneys (ECD n=53, DCD n=11, SCD n=163). When compared to the SCD group, DGF was significantly more common in the ECD group, and time to lower creatinine levels <3 mg/dL was longer. Additionally, costs of transplantation of ECD kidneys were higher due to longer hospitalisation, and more frequent hospitalisations after transplantation. 1-year survival of ECD vs. SCD kidneys was comparable, although it was lower in a long-term follow-up (21).

AR

The analysis included AR episodes confirmed by a biopsy. Its results demonstrated that they were not more common in the ECD group vs. the SCD group. They were compared depending on the time of occurrence since transplantation, within the first month and subsequent 11 months. Similar conclusions can be drawn from the paper by Kim SM et al. The presence of AR confirmed by a biopsy did not differ statistically between both groups, ECD vs. SCD; however, it was a factor affecting the loss of a transplanted kidney (18). In their material Ferer et al. also confirm higher incidence of AR episodes in a group of ECD. They emphasise the significance of shortening of CIT to minimum in order to improve outcomes. Already at baseline, a kidney from an ECD who is statistically older than a SCD exhibits larger damage to nephrons as a result of arterial hypertension, diabetes and a relatively lower number of nephrons on average, and therefore such an organ is more prone to injury resulting from CIT. Consequently, a number of AR episodes increases (20). Ramalho et al. state that DGF is the only factor that is directly associated with AR, and DGF depends on the donor’s age. However, in his studies he did not observe a statistical difference in the AR incidence among ECD and SCD. In addition, he did not observe the effects of AR on the graft loss and recipient survival (14).

Graft recipient survival

During one-year follow-up performed after kidney transplantation in ECD vs. SCD groups we did not observe a significant difference with regard to recipient survival. After 12 months it was 95.2% vs. 98.6%, respectively. The same outcomes with regard to a ECD vs. SCD comparison were published by Ramalho et al. in their paper. The survival rate among ECD and SCD recipients is similar, and it is 83% vs 82% (p=ns), respectively. He did not observe any correlation between recipient survival and recipient age, duration of renal replacement therapy, a history of arterial hypertension in a donor, cerebrovascular incident as a cause of death, creatinine levels prior to collection of >1.5 mg/dL, PRA 30% and the number of mismatched alleles (14). In their paper Stratta et al. compared parameters after transplantation of ECD and SCD kidneys. No differences were observed with regard to recipient survival, graft survival, incidence of AR, mean creatinine levels and the rate of complications and infections. However, they emphasise the significance of appropriate recipient selection, minimum CIT, continuous perfusion during kidney storage, estimation of the nephron mass and appropriate selection of immunosuppression (delayed introduction of calcineurin inhibitors) (23,24). Despite poorer outcomes for transplantation of ECD kidneys presented in some papers, the risk of death of a patient at the age > 60 yrs treated with HD is twice the one observed after transplantation of an ECD kidney. Such outcomes were presented by Savoye et al. Based on his work it can be concluded that transplantation of an ECD kidney is more favourable than leaving a patient on a waiting list (12). Similar conclusions can be drawn from a study by Ojo et al. transplantation of an ECD kidney significantly prolongs patient survival compared to patients receiving dialysis therapy (11).

Graft survival

There is a vivid discussion regarding appropriate allocation of kidneys from ECD in order to provide the best outcomes of treatment. Many issues affecting graft survival have been mentioned. Factors depending on donors, recipients, organ storage and their interactions have been discussed (24-31, 24). Based on the material from our centre we did not observe any statistically significant differences with regard to graft survival: 87.5% for ECD vs. 92.3% for SCD. In their work Fraser et al. (15) compare 5-year survival rates for kidneys from ECD vs. SCD donors. They are similar in both groups, 79.1% vs. 80.5%, respectively. This paper draws attention to arterial hypertension in a donor and ischaemic heart disease as factors that significantly affect the graft survival rate in older kidney recipients (15). On the other hand, Ferrer et al. presents different results of their studies. The analysis included 100 recipients of ECD kidneys and 309 recipients of SCD kidneys. Follow-up tests were performed one year and 3 years after transplantation.
Outcomes are less favourable in the ECD group: 82% vs. 91% after a year, and 75% vs. 84% after 5 years. Factors affecting insufficiency of a transplanted organ include: recipient’s age, CIT, AR and DGF (21). Creatinine clearance, creatinine reduction

At an endpoint of our 12-month follow-up the creatinine levels in patients who received ECD kidneys were slightly higher, although this difference was not statistically significant. ECD vs. SCD 1.9 mg/dL vs. 1.64 mg/dL. When functions of ECD kidneys are compared to SCD kidneys it can be observed that dynamics of the plasma creatinine level reduction is lower. On the other hand, a statistically significant difference with regard to the creatinine clearance was observed. The creatinine clearance in the SCD group was higher than in the ECD group (p<0.05). In his studies Robert J Stratta demonstrates that the eGFR calculated according to the Modification of Diet in Renal Disease (MDRD) formula is higher in the case of SCD kidneys (23,24). In their analysis Fraser et al. presents studies in a group of 234 patients who received ECD kidneys and 234 patients with SCD kidneys. In both groups stabilization of renal functions was observed after 6 months and it was possible to observe higher creatinine levels in ECD kidneys (15).

CONCLUSIONS

Despite significantly more common DGF and poorer graft function observed in patients who received ECD kidneys from ECD there were no effects on the one-year survival of grafts or recipients.

As a result of collecting kidneys from ECD the number of kidneys transplanted may significantly increase.

CITE THIS AS


TABLES

Table 1. Donors demographic within both groups
Table 2. Recipient factors between the groups

<p>| TABLE 1. DONORS DEMOGRAPHIC WITHIN BOTH GROUPS |</p>
<table>
<thead>
<tr>
<th>DONORS FACTORS</th>
<th>ECD GROUP (N=43)</th>
<th>SCD GROUP (N=85)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 6</td>
<td>38.3 ± 13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Male</td>
<td>55.8 (24/43)</td>
<td>67 (57/85)</td>
<td>0.24</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>27.9 ± 7.5</td>
<td>24.7 ± 5.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intensive unit care stay (days)</td>
<td>4.2 ± 1.8</td>
<td>4.87 ± 2.99</td>
<td>&lt;0.024</td>
</tr>
<tr>
<td>Stroke %</td>
<td>79 (34/43)</td>
<td>35 (30/85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac arrest %</td>
<td>30 (13/43)</td>
<td>29.9 (25/85)</td>
<td>0.8</td>
</tr>
<tr>
<td>Arine infusion %</td>
<td>82 (35/43)</td>
<td>89 (76/85)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

<p>| TABLE 2. RECIPIENT FACTORS BETWEEN THE GROUPS |</p>
<table>
<thead>
<tr>
<th>RECIPIENT FACTORS</th>
<th>ECD GROUP (N=76)</th>
<th>SCD GROUP (N=156)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.7 ± 14.3</td>
<td>44.2 ± 15.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Male</td>
<td>54 (41/76)</td>
<td>64 (100/156)</td>
<td>0.38</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>25.3 ± 7.1</td>
<td>24.06 ± 9.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Human leukocytes antigens (HLA) mismatches (A,B,DR)</td>
<td>3.5 ± 1</td>
<td>3.6 ± 1</td>
<td>0.9</td>
</tr>
<tr>
<td>Dialysis treatment prior to KTx (months)</td>
<td>44.6 ± 32</td>
<td>43.7 ± 34</td>
<td>0.75</td>
</tr>
<tr>
<td>% New onset diabetes after transplantation (NODAT)</td>
<td>8 (7/165)</td>
<td>7 (8/55)</td>
<td>0.86</td>
</tr>
<tr>
<td>% Hypertension</td>
<td>90 (142/165)</td>
<td>80 (44/55)</td>
<td>0.9</td>
</tr>
<tr>
<td>% Ischemic heart disease</td>
<td>20 (23/165)</td>
<td>10 (5/55)</td>
<td>0.08</td>
</tr>
<tr>
<td>Triple drug immunsupression</td>
<td>100</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>Induction therapy</td>
<td>31.2</td>
<td>32.2</td>
<td>0.84</td>
</tr>
<tr>
<td>Mean hospitalization post KTx (days)</td>
<td>19.1 ± 13</td>
<td>17.5 ± 16</td>
<td>0.35</td>
</tr>
<tr>
<td>Active Rejection %</td>
<td>15.8</td>
<td>9</td>
<td>0.18</td>
</tr>
<tr>
<td>Creatinine clearance at one year post-KTx</td>
<td>37.65 ± 13</td>
<td>51.37 ± 17.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

FIGURES

Figure 1. Episodes of delayed graft function between the groups
Figure 2. Episodes of delayed graft function between the groups
Figure 3. Mean creatinine levels up to one year post-transplantation
Fig. 2. Episodes of Delayed Graft Function Between the Groups

Fig. 3. Mean Creatinine Levels Up to One Year Post-Transplantation

Bibliography


